

POSITRON EMISSION TOMOGRAPHY OF THE LUNG - INITIAL EXPERIENCES

Per Wollmer



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OF THE LUNG - INITIAL EXPERIENCES

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Abstract Positron emission tomography enables the distribution of positron emitting isotopes to be imaged in a transverse plane through the body and the regional concentration of the isotope to be measured quantitatively. This thesis reports some applications of positron emission tomography to studies of pulmonary pathophysiology. Measurements in lung phantoms showed that regional lung density could be measured from a transmission tomogram obtained with an external source of positron emitting isotope. The regional, fractional blood volume was measured after labelling the blood with carbon-11-monoxide. Regional extravascular lung density (lung tissue and interstitial water per unit thoracic volume) was obtained by subtracting fractional blood volume from lung density. Measurements in normal subjects revealed large regional variations in lung density and fractional blood volume in the supine posture. Extravascular lung density showed a more uniform distribution. The technique has been used to study patients with chronic interstitial pulmonary oedema, pulmonary sarcoidosis and fibrosis, pulmonary arterial hypertension and patients with intracardiac, left-to-right shunt. Tomographic measurements of pulmonary tissue concentration of radionuclides are difficult, since corrections for the blood content and the inflation of the lung must be applied. A simultaneous measurement of lung density and fractional blood volume allows such corrections to be made and the extra-vascular tracer concentration to be calculated. This has been applied to measurements of the tissue penetration of carbon-11-labelled erythromycin in patients with lobar pneumonia.		
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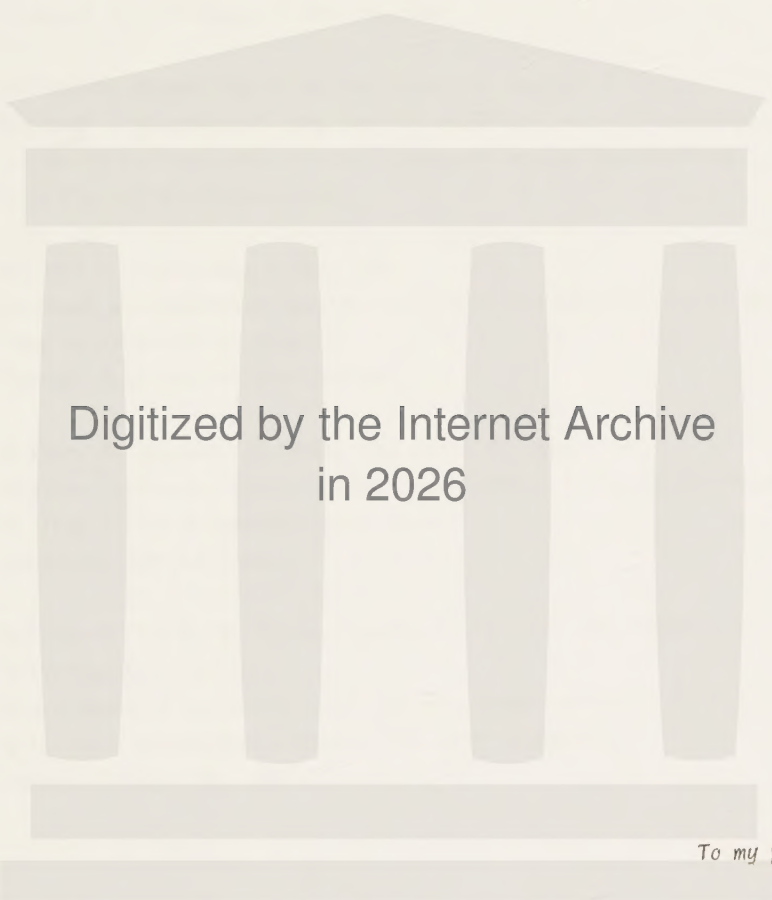
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POSITRON EMISSION TOMOGRAPHY OF THE LUNG - INITIAL EXPERIENCES

PER WOLLMER



LUND 1984



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To my parents

"Science moves but slowly, slowly, creeping on from point to point"

Lord Tennyson

The present thesis is based on the following papers which will be referred to in the text by their Roman numerals.

- I Rhodes CG, Wollmer P, Fazio F, Jones T
Quantitative measurement of regional extravascular lung density using positron emission and transmission tomography
J Comput Assist Tomogr 5:783-791, 1981
- II Wollmer P, Rhodes CG, Allan RM, Maseri A, Fazio F
Regional extravascular lung density and fractional pulmonary blood volume in patients with chronic pulmonary venous hypertension
Clin Physiol 3:241-256, 1983
- III Wollmer P, Rhodes CG, Hughes JMB
Regional extravascular density and fractional blood volume of the lung in interstitial disease
Thorax. Accepted for publication
- IV Wollmer P, Rozkovec A, Rhodes CG, Allan RM, Maseri A
Regional pulmonary blood volume in patients with abnormal pressure or flow in the pulmonary circulation
Submitted for publication
- V Wollmer P, Pride NB, Rhodes CG, Sanders A, Pike VW, Palmer AJ, Silvester DJ, Liss RH
Measurement of pulmonary erythromycin concentration in patients with lobar pneumonia by means of positron tomography
Lancet 2:1361-1364, 1982



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INTRODUCTION

Radioactive isotopes offer a means for non-invasive evaluation of lung function. Although the first studies in man utilized the photon emitting isotope ^{133}Xe (Knipping et al 1955), most of the early measurements of regional lung function were made with positron emitting isotopes. The application of these techniques was limited to a few centers with access to a cyclotron, but with the technical and radiochemical development in nuclear medicine during the 1960s, alternative techniques for assessing regional lung function by means of single photon emitting isotopes soon evolved. Lung scintigraphy has proved of great clinical value and is now widely spread (Fazio and Wollmer 1981).

POSITRON EMITTING ISOTOPES

A positron is an elementary particle with the same mass as an electron, but with a positive, rather than negative, electric charge. Positrons may be emitted from an unstable radionuclide with a relative deficiency of neutrons in the nucleus. The kinetic energy of the emitted positron is rapidly absorbed in tissue after a path length of the order of 1 mm in soft tissue. The positron then interacts with an electron (Fig. 1). The two particles annihilate, and their mass is transformed into the energy of a pair of γ -rays. The γ -rays are emitted at 180° , and each has an energy of 511 keV. Some clinically useful positron emitting isotopes are listed in Table 1. It is of particular interest to find positron emitting isotopes of carbon, nitrogen and oxygen, as these can be incorporated into metabolic substrates and pharmaceuticals without changes in the biochemical properties of the compound. Most of the useful isotopes are cyclotron produced and have a rather short half-life, which limits their use to institutes with a cyclotron available on site.

Table 1. Some clinically useful positron emitting isotopes.

Isotope	T 1/2
Cyclotron produced	
^{11}C	20.1 m
^{13}N	10.0 m
^{15}O	2.1 m
^{18}F	1.7 h
^{19}Ne	17 s
Generator produced	
^{68}Ga	68 m
from ^{68}Ge	275 d

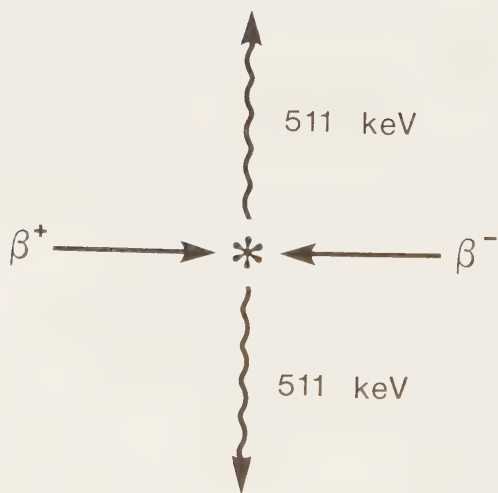


Fig. 1. Positron decay. The positron interacts with an electron, the two particles annihilate and two gamma rays are emitted at an angle of 180° .

COINCIDENCE DETECTION

The positron itself has a short life span and is not readily detected in vivo, but the annihilation γ -rays can be conveniently registered with scintillation counters. The mode of emission of photons in pairs offers considerable advantages. Two detectors placed on either side of an object containing a positron emitting isotope can be connected with an electronic circuit that accepts only pulses which arrive at the two detectors at almost the same time (coincidence detection, Fig. 2A). Such a detection system will only register annihilation events which occur in the space between the two detectors, and thus provides electronic collimation. Another advantage is that the resolution and the sensitivity of the detection system is relatively insensitive to depth. The first pulmonary studies using positron emitting isotopes (Dyson et al 1958) were made with pairs of detectors at the front and the back of the chest. These could be used for coincidence counting or, to obtain higher count rate, parallel counting.

Coincidence detection provides unique possibilities for correction of photon attenuation. If a separate measurement is made with an external source of radiation placed between the object and one detector, one γ -ray will traverse the object. As is illustrated in Fig. 2B, the total path length of the pair of annihilation photons emitted from the external source is identical to that of a pair of photons originating from an annihilation occurring at any depth in the object. The total attenuation of the two gamma rays is thus the same, whether they originate from an organ within the body or from the external source. Furthermore, the photons of different positron emitting isotopes have the same attenuation characteristics. A transmission measurement can thereby be used to measure the tissue attenuation of the annihilation radiation.

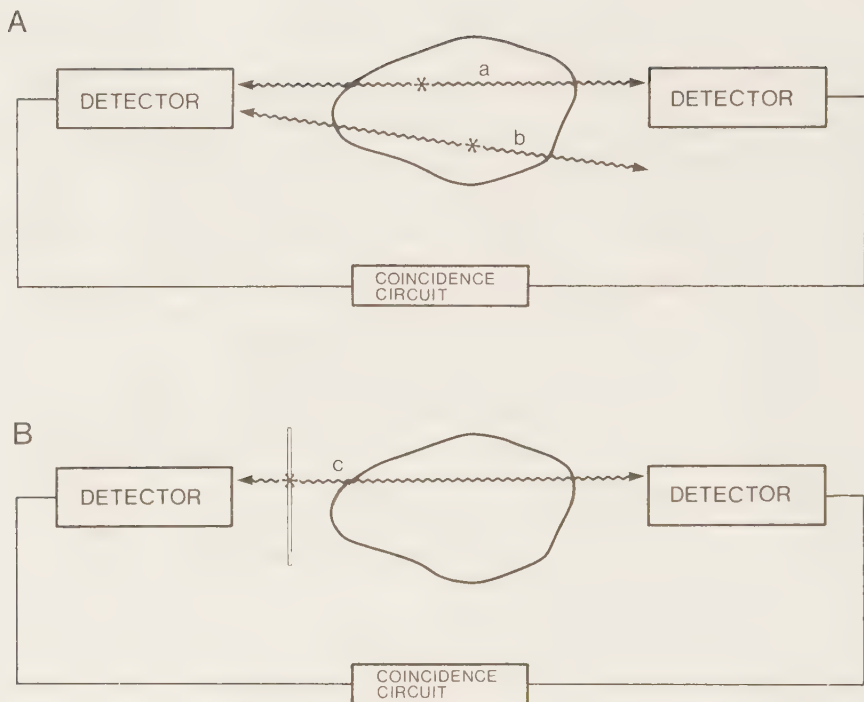


Fig. 2. A. Coincidence detection. Two detectors placed on opposite sides of an object are connected via a coincidence circuit which accepts only pulses that arrive at the two detectors at almost the same time. Only events occurring between the two detectors (a) are accepted.

B. Attenuation correction. A source containing a positron emitting isotope is placed between the object and one of the detectors. One γ -ray traverses the object before hitting the detector. Note that the total path length through the object is the same for pair a and pair c.

EARLY CLINICAL APPLICATIONS

The first positron emitting isotope to be extensively used for studies of pulmonary physiology was ^{15}O (Dyson et al 1958). West and Dollery (1962) were able to show that inhaled labelled carbon dioxide (C^{15}O_2) is taken up exceedingly rapidly in the lung. Through the action of carbonic anhydrase, the oxygen label is exchanged in the water pool in the lung (West and Dollery 1962, Dollery et al 1962). The rate of clearance of the labelled water can be measured with external counters and is linearly related to blood flow (West and Dollery 1960, Dollery et al 1962, Schmidt-Nowara et al 1973). With this technique, West and Dollery (1960) obtained the first regional measurements of pulmonary blood flow in man. They found large regional variations in blood flow in sitting normals, and demonstrated that the distribution of pulmonary perfusion changes with interventions such as changes of posture and exercise. Patient studies revealed profound disturbances of regional pulmonary blood flow in patients with primary lung disease (West et al 1961) as well as in patients with heart disease (Dollery and West 1960, Dollery et al 1961). These findings clearly demonstrated the clinical usefulness of regional measurements of lung function.

Efforts were also made to measure regional oxygen uptake and diffusion properties in the lung using $^{15}\text{O}_2$ and C^{15}O (Dyson et al 1958, Dollery et al 1960), but it was soon realized that the clearance of these compounds is heavily influenced by blood flow (West et al 1962, Schmidt-Nowara et al 1973).

Some information about regional ventilation in the lung can be obtained from the initial distribution of ^{15}O -labelled compounds (West and Dollery 1960), but more accurate measurements of the regional distribution of ventilation is obtained with poorly soluble gases, such as $^{13}\text{N}_2$ (Matthews and Dollery 1965, Rosenzweig et al 1969/70, Ahluwalia et al 1981). Measurements can be made during breath-holding after inhalation of a single breath containing a bolus of $^{13}\text{N}_2$, during wash-in of $^{13}\text{N}_2$ or during the wash-out after $^{13}\text{N}_2$ has been equilibrated in the thoracic gas volume.

Although nitrogen is very poorly soluble, it is possible to produce solutions of $^{13}\text{N}_2$ with such high activity that the solution can be used to measure regional blood flow in the lung after intravenous injection (Clark and Buckingham 1975).

Positron emitting isotopes have also been employed for measurements of the extravascular water pool in the lung. The double indicator dilution technique requires the use of one intravascular tracer and one freely diffusible tracer, e.g. radioactive water (H_2^{15}O). With external detection, information about the regional distribution of extravascular lung water can also be obtained (Fazio et al 1976, Jones et al 1976).

EMISSION COMPUTERIZED TOMOGRAPHY

Detection systems for computerized tomography record disintegrations in one plane (usually transverse) of the body. The thickness of the section studied is dependent on the design of the instrument. The information obtained is fed to a computer and used to reconstruct a tomographic image. In positron emission tomography, photons originating from an annihilation event in the tissue are recorded in coincidence between pairs of detectors organized in a circular or hexagonal array. The reconstructed tomogram shows the distribution of the positron emitting isotope within the plane studied. If an external radiation source containing a positron emitting isotope is placed between the detectors and the object, information about the absorption of γ -rays can be obtained. This can be used to correct the emission tomogram for attenuation, and the corrected emission tomogram then provides quantitative information about the tissue concentration of the isotope (Soussaline et al 1979). The quantitative capability of the positron emission tomograph is related to the finite spatial resolution of the instrument which can be defined by its response (FWHM - full width at half maximum) to a line source of activity. The measured isotope concentration at a given point will be affected, to a varying degree, by surrounding concentration of isotope (partial volume effect). This will result in a loss of accuracy in regions with a size less than twice the FWHM in any direction (Hoffman et al 1979). The resolution of the instrument used in the present studies (ECAT II, EG&G ORTEC; Phelps et al 1978) was 17 mm (FWHM).

POSITRON COMPUTERIZED TOMOGRAPHY OF THE LUNG

MEASUREMENTS OF LUNG DENSITY AND FRACTIONAL BLOOD VOLUME

Development of the technique (I)

Our primary aim of the work with positron tomography of the lung was to develop a technique for measurement of the regional distribution of oedema fluid in man. The regional distribution of extravascular lung water is of interest as regional differences in oedema fluid formation provides information about the relationship between intravascular and interstitial pressure in the lung. Our concept was to measure first the regional density of the lung with a transmission tomogram using an external source of radiation and immediately afterwards the regional blood volume after labelling the blood with ^{11}CO . The difference between these measurements would provide information about the density of the extravascular compartment of the lung.

The relationship between density and picture element counts in the transmission tomogram was studied in a series of phantom studies. We used different materials made up from elements with low atomic numbers to simulate the lung and added water in order to vary the density. The picture element counts were proportional to the density of the phantom in the range 0.02-1 g/ml. Repeated scans were performed in a phantom with a density of 0.28 g/ml to assess the accuracy of the measurement. In a chest phantom with a layer of water simulating the chest wall, we found a small overestimation of lung density, which at least partly can be explained by the partial volume effect.

The fractional pulmonary blood volume was measured after labelling the blood with ^{11}CO by inhalation. An emission scan was obtained, and venous blood was sampled during the measurement. The concentration of ^{11}CO in whole blood was measured in a well counter, and the fractional pulmonary blood volume was obtained by dividing the pulmonary concentration of ^{11}CO (obtained from the picture element counts) with the concentration in whole blood. Lung density and fractional blood volume can be expressed in the same units by taking the density of blood (1.06 g/ml) into account. This allows fractional blood volume to be subtracted from lung density to provide a measurement of extravascular lung density. This reflects the

amount of lung tissue including interstitial water per unit thoracic volume.

Measurements in normal subjects (I, II)

In order to obtain reference values for lung density, fractional blood volume and extravascular lung density, we studied 19 normal volunteers. Illustrative tomograms from one normal subject are shown in Fig. 3.

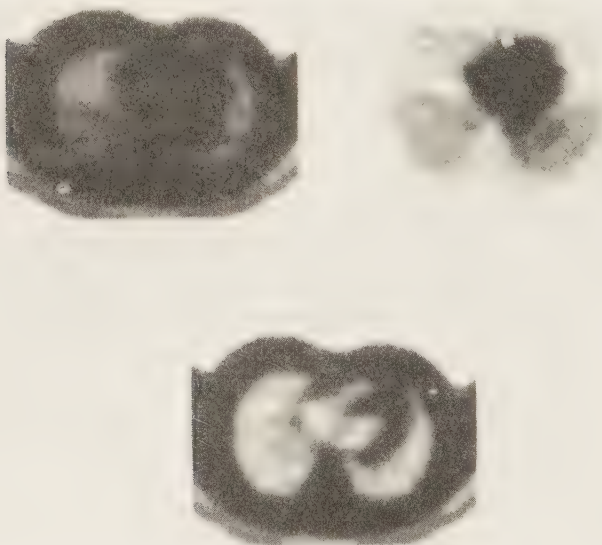


Fig. 3. Tomograms of lung density (top left), fractional blood volume (top right) and extravascular lung density (bottom) from a normal subject.

A constant finding in supine subjects was a ventrodorsal gradient in lung density with mean values of 0.24 g/ml ventrally and 0.40 g/ml dorsally (Fig. 4). The ventrodorsal distribution of fractional blood volume in the supine position is characterized by a ventral plateau at 0.08 ml/ml, which rises steeply in the central part of the lung to a second plateau at 0.21 ml/ml. The distribution of fractional blood volume in normal lung

is mainly determined by the transmural pressure in the vascular bed (i.e. the difference between intravascular and perivascular pressures) and of the elastic properties of the pulmonary vessels. The transmural pressure will vary regionally as a result of hydrostatic effects, whilst the elastic properties are likely to be homogenous in the normal lung. Thus, the observed ventrodorsal gradient of fractional blood volume in normal subjects may be a consequence of the effect of gravity on the transmural pressure.

Most of the ventrodorsal gradient seen in lung density is accounted for by the regional differences in fractional blood volume. The extravascular density shows a minor, uniform ventrodorsal gradient, rising from 0.12 g/ml in the ventral part to 0.16 g/ml in the dorsal part. This gradient could be explained by regional differences in lung expansion due to the influence of gravity (Glazier et al 1967).

Measurements in patients with pulmonary oedema (II)

As a model of pulmonary oedema, patients with cardiomyopathy and chronic pulmonary venous hypertension were studied. We found increased extravascular lung density in the patients. The increase was non-uniform with the greatest abnormalities seen in the dorsocaudal part of the lung (Fig. 4). In this group of patients, increased extravascular lung density not only reflects the accumulation of interstitial or alveolar fluid, but also the structural abnormalities that develop in the lung parenchyma and vasculature with long standing pulmonary venous hypertension (Heath and Edwards 1959). However, without the introduction of an extracellular or cellular marker, it is not possible to differentiate between increased tissue mass and the accumulation of interstitial or alveolar fluid as a cause of increase extravascular lung density.

A problem with the interpretation of changes in extravascular lung density is their relation to lung expansion - since a reduction in lung expansion should automatically be associated with an increase in extravascular lung density. A possible way to account for lung expansion is to take the ratio between extravascular lung density and fractional blood volume, as this ratio is likely to be less affected by moderate changes in lung expansion. Similar ratios have been used by other workers as a measure of pulmonary

oedema (Fazio et al 1976, Binswanger et al 1978, Hales et al 1981). The increase in the ratio of extravascular lung density to fractional blood volume also showed a dependent distribution.

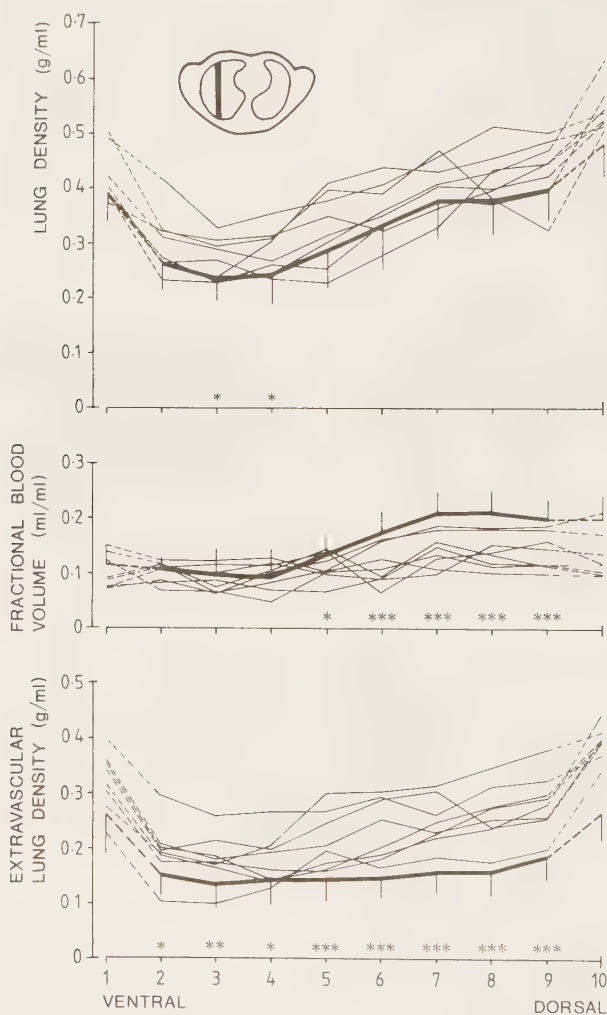


Fig. 4. Ventrodorsal profiles of lung density, fractional blood volume and extravascular lung density. A 1.7 cm wide region was chosen in the middle of the right lung (inset). Thick lines denote mean of 19 normal subjects and vertical bars one SD. Thin lines represent individual patients with chronic pulmonary venous hypertension. Points 1 and 10 are influenced by "spillover" from the chest wall. Asterisks denote significant deviations from normal: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The finding of a gravity dependent distribution of regional extravascular lung density may be explained by the relationship between pressure gradients in the lung. It is well established that there is an intravascular pressure gradient down the lung, but regarding perivascular pressure, most of the available information is indirect (Staub 1980). A gravity dependent distribution of oedema fluid implies that net fluid filtration is higher in the dependent parts of the lung. This could be caused by an increase in the perivascular pressure in the direction of gravity that is smaller than the intravascular hydrostatic pressure gradient in the oedematous lung.

Fractional blood volume is a measurement of the volume of blood per unit thoracic volume and includes blood contained in intrapulmonary vessels only. In comparison, measurements of pulmonary blood volume obtained by means of indicator dilution techniques include also extrapulmonary vessels. Measurements of the capillary blood volume of the lung can be obtained from measurements of the transfer factor for carbon monoxide.

Fractional blood volume was reduced in patients with chronic pulmonary venous hypertension (Fig. 4), which may be explained by reactive structural changes in the vessels or reduced transmural pressure due to perivascular oedema.

Measurements in patients with "interstitial" lung disease (III)

Extravascular lung density encompasses lung tissue as well as interstitial water, and may be used as a measure of the abnormalities occurring in "interstitial" disease - i.e. oedema, accumulation of inflammatory cells, formation of granulomata and fibrosis (Crystal et al 1981). Measurements were performed in one group of patients with sarcoidosis having mild to moderate functional impairment and in one group of patients with pulmonary fibrosis of varying etiology having severe functional impairment. Extravascular lung density was increased in all patients, and large regional variations were observed. In two patients with sarcoidosis, a reduction in extravascular lung density was observed after steroid treatment. This was associated with radiographic and functional improvement and demonstrates the feasibility to measure quantitatively the response to treatment of sarcoidosis.

Fractional blood volume was within normal limits in most patients with sarcoidosis of mild to moderate degree, but was reduced in all patients with pulmonary fibrosis. It is well known that there is a reduction in capillary blood volume in patients with severe fibrosis (McNeill et al 1958, Bates et al 1960, Hamer 1963, Saumon et al 1976). The magnitude of the reduction we observed in fractional blood volume shows that larger vessels as well as capillaries are affected.

Measurements in patients with increased pulmonary blood flow or pulmonary arterial hypertension (IV)

The regional distribution of pulmonary blood flow has been studied extensively in relation to regional vascular pressure (see West 1977 for references). A model has evolved, which relates regional blood flow to arterial, alveolar and venous pressures (Banister and Torrance 1960, Permutt et al 1962, West et al 1964, West and Dollery 1965). Although this model implies regional changes in blood volume with changes in flow and vascular pressure, little information has been obtained about the regional distribution of blood volume in man.

We studied the effect on regional fractional blood volume of chronic increase in flow (patients with intracardiac left-to-right shunt without appreciable pulmonary hypertension) and chronic increase in pressure (patients with Eisenmenger's syndrome or primary pulmonary hypertension). The distribution of fractional blood volume was more uniform in both groups of patients than in normal subjects. This may be explained by recruitment (Maseri et al 1972) and/or distension (Glazier et al 1969) of vascular beds. In patients with chronic increase in flow, we found indications of an over-all increase in intrapulmonary blood volume, whereas patients with severe pulmonary hypertension did not differ from normal subjects in this respect. Longstanding hypertension is likely to be associated with reactive vascular changes reducing the compliance of the vascular bed, and possibly obliteration of capillary beds.

Measurement of tracer concentration in the extravascular compartment of the lung (V)

The isotope concentration measured with a positron tomograph refers to the amount of activity per unit thoracic volume. In the physiological and pharmacological context, the concentration of a tracer must be expressed with respect to its volume of distribution. With the technique for measuring lung density and fractional blood volume, the volume of three compartments can be measured: (i) gas volume ($1 - \text{lung density}/1.06$), (ii) intravascular compartment and (iii) the extravascular lung compartment (which includes the intracellular and interstitial compartment). The distribution of the tracer may not be confined solely to the compartment of interest, and activity in any other compartment then constitutes a background which needs to be subtracted. For this purpose, the background activity must be expressed in terms of thoracic concentration and subtracted from the total thoracic concentration of the tracer. If, for example, the concentration of a tracer in the extravascular compartment is to be measured, the signal from circulating tracer must be subtracted. A measurement of the vascular concentration of the tracer can be obtained from a measurement of pulmonary blood volume and the blood concentration of the tracer, as measured from a blood sample or a sufficiently large region of interest in the heart or the aorta.

This concept has been applied to measurements of the concentration of labelled erythromycin in a pharmacokinetic study in patients with lobar pneumonia. The drug was labelled with ^{11}C without altering its biochemical characteristics (Pike et al 1982). A transmission tomogram provided a measurement of lung density and information for attenuation correction of the ensuing emission scans. Two to four mCi of labelled erythromycin were administered intravenously in a total dose of 270 mg erythromycin lactobionate. The concentration of erythromycin was measured during 60 minutes after the injection. Finally, ^{11}CO was used to obtain a measurement of fractional blood volume. A correction for circulating erythromycin was made by normalizing the blood volume tomogram to the count density of labelled erythromycin in arterial blood as measured from a region in the aorta or the left heart. Normalized in this way, the blood volume tomogram provides a measurement of the intravascular concentration of erythromycin. After subtraction of erythromycin in the vascular pool, a measurement of the amount of erythromycin per unit

thoracic volume was obtained ($\mu\text{Ci}/\text{ml}$). By dividing this with extravascular lung density (g/ml), the concentration of erythromycin in the extravascular compartment was obtained ($\mu\text{Ci}/\text{g}$). In the pneumonic lung, extravascular lung density includes lung tissue, interstitial fluid and any alveolar fluid.

The mean concentration of erythromycin in the pneumonic lung during the period of measurement was $5.5 \mu\text{g}/\text{g}$. This was not significantly different from the $6.6 \mu\text{g}/\text{g}$ observed in the control lung. The clearance of activity from the blood, and the accumulation in the pneumonic lung are shown in Fig. 5. Penetration to the extravascular space is rapid, near maximum concentration being reached within 10 minutes after injection. Equilibration between the concentration in blood and in the extravascular space was reached after approximately 45 minutes and thereafter erythromycin was slowly washed out from the extravascular space.

Hence, there is a rapid uptake of erythromycin in pneumonic lung after the intravenous injection of the drug. Moreover, the penetration is as effective in pneumonic regions as in normal lungs. The concentrations achieved in pneumonic regions after injection of 270 mg of erythromycin are well above the minimum inhibitory concentration for most sensitive organisms.

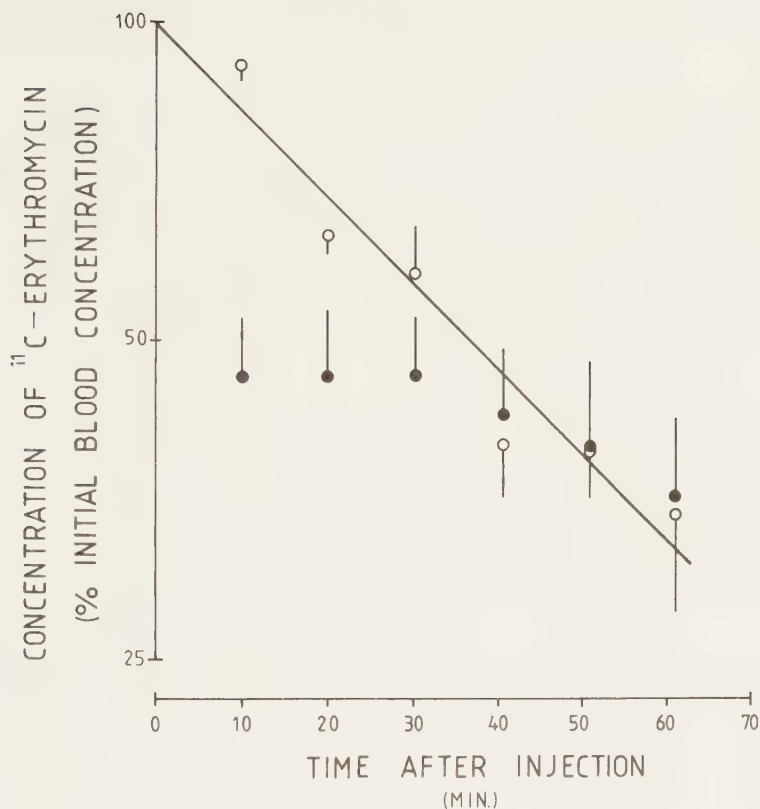


Fig. 5. Blood clearance and uptake of ^{11}C -erythromycin into the extra-vascular compartment of the pneumonic lung.
 Open circles = mean $\pm$ SE of arterial blood concentration in five patients.
 Equation: $\ln y = -0.019x + 4.60$, $r = -0.96$
 Closed circles = mean $\pm$ SE of extravascular concentration in pneumonic lungs.

CONCLUDING REMARKS

Positron emission tomography enables the regional thoracic concentration of positron emitting isotopes and the regional density of the lung to be measured quantitatively. This concept has been used to measure abnormalities in the lung in terms of extravascular lung density and fractional pulmonary blood volume, providing new clinical information about the pathogenesis of common diseases like pulmonary oedema, "interstitial" lung disease and intracardiac shunt.

Pharmaceuticals as well as metabolic substrates can be labelled with positron emitting isotopes without changing their biochemical characteristics, and their concentration measured in vivo. In combination with measurements of lung density and fractional blood volume, their distribution in different compartments can be measured, as is demonstrated by the study of the pharmacokinetics of erythromycin. The pulmonary handling of certain pharmaceuticals, such as amines, may be interpreted in physiological terms, and studies of their kinetics may provide new information about pulmonary pathophysiology (Pang et al 1982ab, Pascal et al 1982).

The application of positron emission tomography in the lung may also provide a number of other new approaches to the investigation of lung function in health and disease. Radioactive gases are potentially very useful in combination with positron tomography. $C^{15}O_2$ can be used to label the pulmonary water pool (Ahluwalia et al 1980) or to provide information about the ventilation-perfusion relationship in the lung (Nichols et al 1978, Wollmer et al 1982). Quantitative values of regional ventilation-perfusion ratio can be obtained by measurements during continuous infusion of ^{13}N in solution (Wollmer et al 1982) and regional specific ventilation can be measured quantitatively using the short-lived radioisotope ^{19}Ne (Crouzel et al 1980, Valind et al 1982).

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Quantitative Measurement of Regional Extravascular Lung Density Using Positron Emission and Transmission Tomography

Christopher G. Rhodes, Per Wollmer, Ferruccio Fazio, and Terry Jones

Abstract: A technique has been developed to measure regional values of vascular and extravascular lung density using positron emission and transmission tomography. Quantitative values of lung density in a transaxial plane are obtained by recording transmission scans during the exposure of a ring source of positron emitting germanium/gallium-68, which encircles the subject in the plane of the scan. Values of blood density are obtained by scanning in the emission mode following the labelling of the subject's red blood cells with a quantity of ^{14}C -carbon monoxide inhaled as a bolus. Subtraction of the normalised blood volume scan from the normalised lung density (transmission) scan provides regional values of extravascular lung density. The response of the transmission scan to changes in density was obtained by scanning different tissue equivalent materials in the density range 0.02 to 1.0 g cm^{-3} . This resulted in a linear relationship between pixel counts and density. Density measurements made *in vitro* on simulated chest phantoms suggest that, at worst, random errors of 3.5% and systematic errors (due to the influence of the chest wall) of between 10 and 15% will be incurred when measurements are made *in vivo* on lungs of average normal density (0.3 g cm^{-3}). The random error associated with the emission scan (arising from counting statistics alone) was found to be 1.2%. Measurements of lung density made on five normal subjects (supine) resulted in a mean density of 0.29 g cm^{-3} for a region in the lower (caudal) part of the lung, with a range of values between 0.26 and 0.32 g cm^{-3} from subject to subject. A pronounced anteroposterior gradient of both lung density and blood density was observed, while the gradient of extravascular lung density was quite small. The mean value of the ratio extravascular:vascular lung density for both caudal and cranial lung regions was 0.92 ± 0.25 . **Index Terms:** Lungs—Lungs, blood supply—Emission computed tomography—Computed tomography.

Two-thirds of the volume occupied by a normal healthy lung is air. Consequently, it is possible for this organ to undergo large density changes (-100 to $+200\%$), which, if measured, could provide a sensitive index of abnormality in both primary and secondary lung disease. However, it is clear that any changes in overall lung density are the result of individual variations in the density of the vascular and extravascular compartments, and that a modest increase in the density of one could be masked by a corresponding decrease in the density of the other.

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An essential prerequisite of any technique concerned with the measurement of pulmonary density, therefore, is that it is able to differentiate between vascular and extravascular compartments.

Available techniques for the regional measurement of lung density or water pool size range from the simple and qualitatively sensitive chest radiograph (1,2) to more quantitative techniques including computer assisted transmission tomography (CT) (3-6), Compton scatter techniques (7-9), transthoracic gamma ray attenuation (10), and tracer dilution techniques (11-13).

While the quantitative ability of CT has recently been established for materials in the soft tissue density range (14), there has been little investigation into its response to materials in the low density

range ($0\text{--}0.7\text{ g cm}^{-3}$) where beam hardening artifacts may be a problem (15). Furthermore, this technique cannot quantitatively differentiate between vascular and extravascular compartments in the peripheral lung. Compton scatter techniques, although possibly less expensive to support than CT, are generally inferior both in terms of resolution and accuracy (16). However, attempts have been made, using a nontomographic form of this approach, to quantitate the vascular pool (8). Indicator dilution techniques that rely on the injection of diffusible and nondiffusible tracers are able to differentiate between the vascular and extravascular water pools, but they are associated with theoretical and practical problems of analysis (13), and are not, in general, amenable to use with tomography. Furthermore, no entirely satisfactory way has yet been established for the normalisation of regional water pools, which, to date, have been expressed as lung water per unit blood volume or blood flow (11).

The positron emission tomograph, which can be used in both the emission and transmission mode, relies on the coincidence detection of paired monoenergetic annihilation gamma rays (511 keV) and, for this reason, does not suffer from beam hardening effects. This provides an opportunity to obtain accurate values of vascular and extravascular lung density by using both density and tracer measurements. In this paper, we show how positron emission and transmission tomography can be used to measure lung density (vascular plus extravascular— g cm^{-3}), vascular density ($\text{ml (blood) cm}^{-3}$), and extravascular lung density (tissue plus water— g cm^{-3}). The results of measurements made on five healthy normal volunteers are shown.

THEORY

Measurements are made using a positron emission computer assisted tomograph (ECAT) in both the emission and transmission modes. The transmission scan, which is routinely performed to correct emission scans for attenuation effects, results in an image that is a tomographic distribution of tissue density. This scan provides the lung density distribution. The blood volume distribution is obtained by performing an emission scan following the inhalation of a quantity of ^{14}C -labelled carbon monoxide (^{14}CO). (Alternatively, if ^{14}C is unavailable, the generator-produced ^{68}Ga could be used, bound to transferrin, as a short-term vascular marker—albeit at a greater radiation dose to the subject). The extravascular lung density distribution is then obtained by subtracting the normalised blood volume scan from the normalised transmission scan.

Lung Blood Volume Distribution

The inhalation of a quantity of ^{14}CO provides a simple way of radioisotopically labelling the vascular compartment. This results from the formation of ^{14}C -carboxyhaemoglobin in the lung capillaries, which quickly distributes itself within the blood volume of the subject. An emission scan recorded after this period of equilibration will therefore represent the relative blood volume distribution in that section of tissue. An absolute distribution of the fractional blood content [$\text{ml (blood) cm}^{-3}$] can be obtained if the concentration of ^{14}C -carboxyhaemoglobin in the blood is known. This follows, since a linear relationship exists between ECAT picture element counts ($\text{counts sec}^{-1}\text{ pixel}^{-1}$) and isotope concentration ($\mu\text{Ci cm}^{-3}$). (This calibration factor (k_E) has been derived from previous phantom studies performed on the ECAT (17) and is common to all emission scans.) Venous blood samples, taken from a peripheral site during the emission scan, are used to measure the whole blood concentration of ^{14}C -carboxyhaemoglobin (C_{vb}). The product of the blood concentration and k_E results in an image pixel count, which would be recorded in the emission scan had it included a region containing all blood (the heart chambers, for example) large enough to ensure full quantitative recovery, i.e., to overcome the partial volume effect (18). The fractional lung blood volume distribution or blood density scan D_V ($\text{ml (blood) cm}^{-3}$) is then obtained by dividing each element of the emission scan (S_E) by the calculated "whole blood" pixel count, thus:

$$D_V = \frac{S_E}{k_E C_{vb}}$$

Areas in this scan that have values close to unity can be inferred to represent volumes of blood with no extravascular tissue (or air) present. This occurs within the chambers of the heart in a scan recorded at a suitable level through the lower part of the thorax.

Lung Density Distribution

The lung density distribution (vascular plus extravascular) is obtained from the transmission scan taken through the same plane as the emission (^{14}CO) scan. The transmission scan is recorded during the exposure of a ring source of positron emitting ^{68}Ge , which encircles the subject. Before reconstruction, the transmission information is normalised using a blank (air only) transmission scan, which is performed daily. The resulting transmission image is independent of source strength and scan accumulation time and is similar to that of a conventional CT scan but has less spatial resolution. In order to es-

establish the unique accuracy of the "positron" transmission scan for the measurement of lung tissue density, phantom measurements were made using materials with different water:air ratios (damp sawdust) in the range 0.02 to 1.0 g cm⁻³.

To enable a direct comparison between the "density" and blood volume scans to be made, the former must first be expressed as blood density equivalents. This is achieved by dividing each pixel in the transmission scan by a second calibration factor (k_T), which relates transmission pixel counts (counts pixel⁻¹) to blood density equivalents (i.e., 1 blood density equivalent = 1.06 g cm⁻³). This calibration factor is obtained from the transmission scan itself and is the mean pixel count within the boundary of the heart chamber. This region is defined by values of unity in the blood density scan and is usually sited within the right atrium. Denoting the original transmission scan as S_T and the normalised lung density scan (vascular plus extravascular) as $D_{(V+EV)}$ we obtain:

$$D_{(V+EV)} = \frac{S_T}{k_T}$$

Extravascular Lung Density Distribution

The extravascular density distribution (D_{EV}) is obtained by subtracting the blood density scan from the normalised lung density scan. That is

$$D_{EV} = D_{(V+EV)} - D_V \\ = \frac{S_T}{k_T} - \frac{S_T}{k_E C_{Co}}$$

Although the result is a density distribution expressed as blood density equivalents, it can be converted into g cm⁻³ by multiplying each pixel in the scan by the numerical value for the density of blood. This value can either be obtained from tables as a mean for normal subjects (1.060 ± 0.004 g cm⁻³—Geigy Scientific Tables) or calculated as the ratio of k_T to the mean pixel count from a water phantom.

MATERIALS AND METHODS

The measurements were made using an EG&G ORTEC ECAT II scanner. The quantitative capability of this instrument in the *emission* mode is well documented (17) and relies mainly on attenuation measurements made in the transmission mode. These are obtained by scanning the subject during the exposure of a retractable ring source of a positron emitting isotope, which completely encircles the subject in the plane of the tomographic slice. The ring source consists of a circular stainless steel tube 60.3 cm in diameter containing between 2 and 3 mCi of ⁶⁸Ge. A motor drive allows it to be moved

into a shielded position during emission scanning. Since the ECAT records only coincident gamma events (resulting from positron annihilation), the attenuating path length for one member of the photon pair (in the transmission mode) is equal to the local thickness of the subject's body. This path length is also equal to the sum of the path lengths of the photon pair when recorded during an emission scan and thus allows an absolute correction for attenuation to be made. The final attenuation corrected emission scan has a linear response to regional isotope concentration and has no zero offset (i.e., the image pixel counts are related to isotope concentration by a single constant).

In view of the central role played by the transmission scan itself, studies were performed to establish its response to changes in tissue density.

Phantom Measurements

Studies were performed to determine: (a) the relationship between transmission pixel counts and the density of a number of different water:air phantoms in the density range 0.02 to 1.0 g cm⁻³; (b) the effect on density measurements of surrounding a lung tissue equivalent material with water; and (c) the statistical variation of both transmission and emission measurements obtained by repeatedly scanning lung tissue equivalent phantoms.

In the first phantom study, expanded polystyrene, synthetic foam, sawdust, and water were used in various proportions to give mixtures with densities in the range 0.02 to 1.0 g cm⁻³. These mixtures were scanned in a light polyethylene container of known weight and volume. The weight of the container plus mixture was determined before each scan—no significant loss of water from the damp materials occurred during scanning. A polyethylene bottle containing water was then scanned to give a mean "water pixel count" with which to normalise the variable density phantom.

In the second study, a cork block (of density 0.31 g cm⁻³) was submerged in a tank of water. The dimensions of the cork (14 × 8 cm in the plane of the scan) were chosen to be similar to those of a small lung in the anteroposterior plane. The block, which was surrounded by at least 6 cm of water, was supported by two thin walled, water filled plastic containers. Density measurements were made with and without the surrounding water.

The third phantom study entailed scanning a chest phantom containing a heart, chest wall, and vertebral column of unit density material and a lung compartment (damp sawdust) of density 0.28 g cm⁻³. Measurements were made first in the emission mode with ⁶⁸Ga mixed throughout the lung compartment. Fifteen emission scans were recorded, each with a progressively longer accumulation time to

compensate for the decay of the isotope ($T_{1/2}^{68\text{Ga}} = 68 \text{ min}$). The isotope concentration and the duration of the first scan were chosen to give a count density of approximately 2,900 counts per pixel. This count density is comparable to those found in the blood volume scans of normal lungs and would be the pixel count obtained for a ^{11}CO blood concentration of a $0.90 \mu\text{Ci ml}^{-1}$, a lung blood density of 0.16 ml cm^{-3} , and a scan time of 15 min. When the ^{68}Ga had decayed to a negligible level, 15 transmission scans, each of 15 min duration, were recorded with the chest phantom in the same position. The emission scans were each reconstructed using a different transmission scan. The statistical variation of repeated measurements made in the emission and transmission modes was calculated using a common region of interest, 2.7 cm^2 in area, situated at the centre of the lung. The size of this region of interest was chosen to be representative of the smallest of those used in the analysis of the human studies.

Lung Density Measurements

Measurements of lung density were made on five healthy young normal volunteers. The subjects were positioned (supine) such that scans could be made at standard positions: one around the fourth rib (well clear of the diaphragm), the other 8.5 cm toward the head. After a period of time had elapsed to allow settling of the subject's respiration rate, heart rate, and posture, the ring source was exposed and a 15 min transmission scan was recorded at

each level. This resulted in an average accumulation of 10 million true coincidence counts per scan. Following the transmission scanning, ^{11}C -carbon monoxide was administered, over a period of 1 to 2 min, by direct infiltration into the subject's inspired air using a common disposable face mask. This manoeuvre labels the subject's blood with approximately 9 mCi of ^{11}C -carbon monoxide, which results in a vascular concentration of the order $1.7 \mu\text{Ci ml}^{-1}$ and a radiation dose to the blood of approximately 650 mrad. During the period of equilibration (5 min), a butterfly needle was placed in a hand vein for the sampling of blood. Emission scans were then recorded for 15 min at each lung position, while six blood samples were taken for the measurement of ^{11}C -carboxyhaemoglobin. The blood activity was measured in a calibrated NaI well counter. The mean of three samples taken during each emission scan was used to calculate the fractional blood volume distribution and, in turn, the extravascular lung density distribution, as described above.

RESULTS

Phantom Measurements

The relationship between the normalised pixel count and the measured physical density for different variable density water phantoms is shown in Fig. 1. The points all lie close to the line of identity (shown) resulting in a linear response with negligible offset at zero density. Regression analysis was used to find the line of best fit and resulted in a calculated slope of 0.987, an intercept of 0.637 (%), and a correlation coefficient of 0.9998.

The effect of a scattering medium on the measurement of density is shown in Fig. 2. A horizontal strip 1.7 cm wide was used to calculate the density profile through the cork block, water, and perspex tank wall. Subtraction of the two profiles (derived from measurements made with and without water in the tank) results in a background or "error" profile. The central region of this profile, corresponding to the 14 cm of cork and shown as open circles in Fig. 2, was subject to the standard strip analysis that divides the region into 10 subregions. [Because of spatial resolution effects arising from the proximity of the chest wall (see Discussion), only the central eight subregions are used in the analysis of lung density in the human studies.] The effective background pixel count for the centre of the strip (subregions 5 and 6) and the edge of the strip (subregions 2 and 9) are 3.0 and 4.6% (water), respectively.

The repeated transmission scanning of a chest phantom containing lung tissue equivalent material (damp sawdust) of density 0.28 g cm^{-3} resulted in a range of pixel counts, from scan to scan, with a

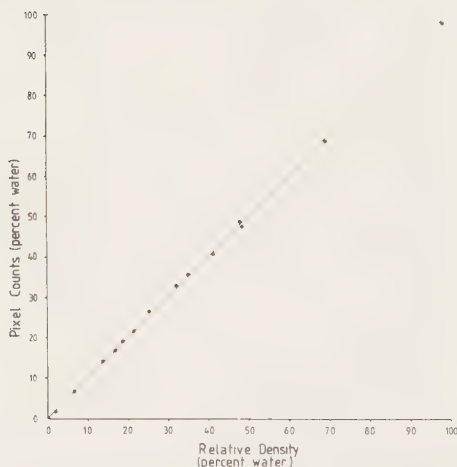


FIG. 1. ECAT transmission calibration curve obtained by scanning materials of different density. Results of linear regression analysis: slope, 0.987; intercept, 0.64%; r , 0.9998.

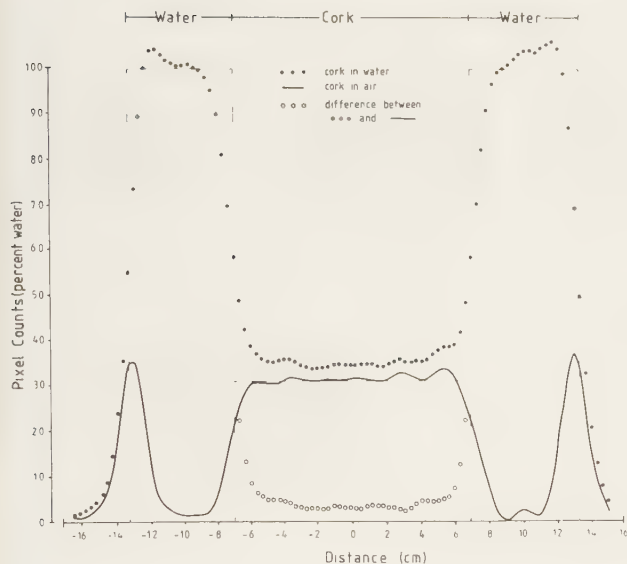


FIG. 2. Density profiles through a cork phantom, with and without water. The thin continuous line represents the position and relative density of the cork and water. (The two peaks observed in the cork in air profile result from the thin perspex walls of the empty water tank. This also explains the nonuniform shape of the profile through water as perspex has a density approximately 25% greater than that of water.)

standard deviation of 3.5% for a scan time of 15 min. The area of the region of interest was 2.7 cm². Moving the region of interest to the heart area of this phantom (a water container) resulted in a range of pixel counts with a standard deviation of 1.1%. The repeated emission scanning of the chest phantom with ⁶⁸Ga present in the lung compartment (equivalent to a radioactive concentration of 0.14 μ Ci cm⁻³ for a scan time of 15 min) resulted in a range of pixel counts with a standard deviation of 1.2%.

Lung Density Measurements

Normalised images of lung density, blood volume, and extravascular lung density are shown for caudal and cranial (caudal +8.5 cm) lung regions of a single subject in Fig. 3. A nonlinear grey scale has been used for the density range 0 to 1.0 g cm⁻³ to emphasise the differences in the low density values of the lung.

The images were analysed in two ways and, because of its size, information from the left lung was not included. A rectangular region of interest, approximately 1.7 cm wide, was drawn from the anterior to posterior chest wall in each of the three caudal plane scans. This strip, which varied in length from subject to subject, was then divided into 10 equal subregions or segments from each of which was calculated the mean pixel count. The results of measurements made on five normal, healthy,

nonsmoking subjects (aged 32 ± 5 years) are shown in Fig. 4.

The anteroposterior variation in lung density is characterised by an initial plateau at a density of 0.20 g cm⁻³, which rises steeply in the central part of the lung strip to a value of 0.38 g cm⁻³ posteriorly. These changes of density result in a maximum gradient, between the fourth and seventh segment, of 0.053 g cm⁻³ segment⁻¹. Because the values of lung density at the extreme ends of this region of interest are affected by the presence of the chest wall, by virtue of the "spillover" of pixel counts from the chest wall area to the lung area, segments 1 and 10 have been excluded from the calculation of mean lung density. The mean value of lung density for the remaining eight segments, in the five normal subjects, is 0.29 ± 0.08 g cm⁻³ (1 SD). The range and standard deviation of the mean values of lung density, from subject to subject, are ± 0.03 and ± 0.02 g cm⁻³, respectively.

The variation in blood density (Fig. 4) follows a similar pattern to that of lung density with values rising from 0.075 ml cm⁻³ anteriorly to 0.21 ml cm⁻³ posteriorly. This again results in a maximum gradient between the fourth and seventh segment with a value of 0.046 ml cm⁻³ segment⁻¹. In contrast, however, the extravascular gradient of lung density (Fig. 4) is much reduced, rising from a value of 0.12 g cm⁻³ anteriorly to 0.16 g cm⁻³ posteriorly. The maximum gradient is now only 0.012 g cm⁻³ segment⁻¹, spread uniformly between the third and ninth segment.

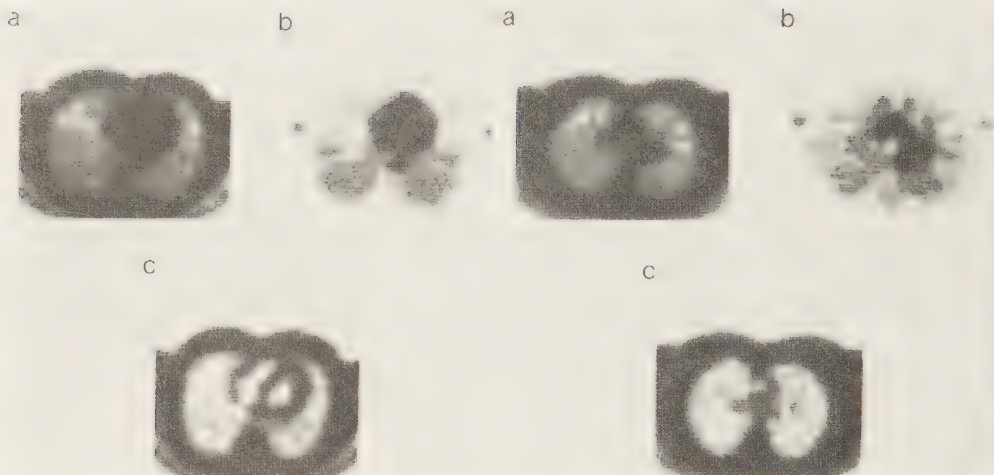


FIG. 3. Axial transverse tomographic images of lung density (a), blood density (b), and extravascular lung density (c) in caudal (left) and cranial (right) lung regions of a normal subject. An eight level exponential grey scale between 0 and 1.0 g cm^{-3} has been used to emphasise the differences in the low values of lung density.

The second analysis was concerned with possible caudal to cranial differences and required the delineation of a central, elliptical region of interest in the cranial lung scan that could be projected onto the lower (caudal) scan at the same vertical height (i.e., the same gravitational level). This lower region was then shifted sideways to delineate the corresponding position midway between the mediastinum and the chest wall. The results (Fig. 5) show only small differences in lung density, blood volume, and extravascular lung density between the caudal and cranial planes, with an extravascular lung density:blood volume ratio (caudal plus cranial) of 0.90 ± 0.25 .

DISCUSSION

The use of the transmission scan is central to our measurement of lung density and stems from its important and unique role as a means of correcting emission scans for the absorption effects caused by body structures. Its use is in preference to that of a water tracer (H_2^{15}O) because it has a high signal to dose ratio (the dose from the ^{68}Ge ring source during a transmission scan is $40 \text{ mrad s hr}^{-1}$ in air). In addition, because density and not exchangeable water volume is measured, the technique has the ability to detect those extravascular compartments that have a low exchangeable water content, and those regions with an abnormally low ventilation or perfusion that would not be labelled to equilibrium

with inhaled or injected tracers in first pass dilution techniques. However, this does mean that the technique is unable to differentiate between exchangeable extravascular water pools and nonexchangeable extravascular tissue masses (pulmonary oedema and fibrosis, for example).

Phantom Measurements

The hypothesis that the transmission scan could provide values of tissue density was adequately proven by the results of the phantom study (Fig. 1). These show a one-to-one relationship, with little zero offset, between changes in the normalised pixel count from scans of different phantoms, and changes in their water content. While dry sawdust may not be a true lung tissue equivalent material, it appears to be sufficiently close for it to represent normal lung tissue when water is added (the mean water content of an equal lung tissue:blood mixture is approximately 82%). This supposition is supported by the position of the three lowest points in Fig. 1, obtained by scanning dry sawdust, synthetic foam, and expanded polystyrene, all of which lie very close to the line of identity. This suggests that materials made up of elements with low atomic numbers have absorption coefficients (for 511 keV gamma rays), which bear a proportional relationship to their density.

The random error of $\pm 3.5\%$ (1 SD) associated with transmission scanning a phantom of density

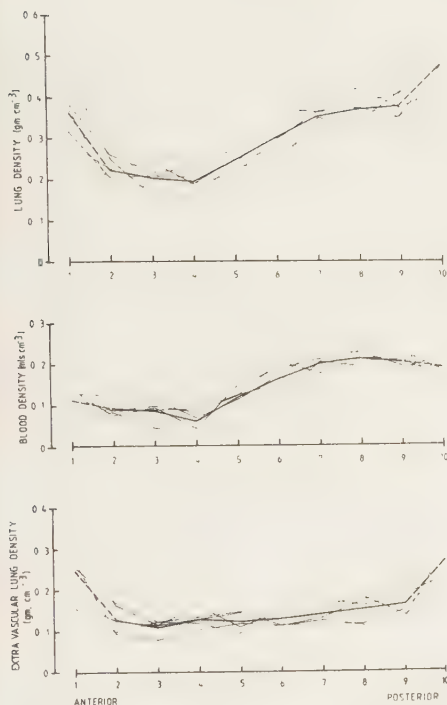


FIG. 4. Anteroposterior profiles of lung density, blood density, and extravascular lung density in five normal subjects (mean values are denoted by the heavy line) obtained from the subdivision of a 1.7 cm wide strip region of interest drawn through the right lung of the caudal plane scan.

0.28 g cm^{-3} , with a region of interest 2.7 cm^2 in area, is acceptable and is of the same order of magnitude as the random error associated with the emission scan [1.2% (1 SD) for a 2.7 cm^2 lung region] following the administration of 9 mCi of ^{11}CO .

In addition to the statistical uncertainties described above, both emission and transmission scans are subject to a spatial resolution phenomenon known as the partial volume effect. This manifests itself in two ways. First, as an inability to differentiate between activity or density distributions that lie less than one resolution distance apart (i.e., $<1.6 \text{ cm}$) because of the spillover of pixel counts from a region of high pixel count density to a region of low pixel count density, and second, as an apparent reduction in the density of a structure or the reduction in the concentration of an isotope in a region that occupies a volume less than 3.2 cm in any direction (18). This means that lung regions that lie within 1.6 cm of the chest wall or heart cannot be analysed with any reasonable degree of accuracy. Lung regions that lie further away from chest wall are less susceptible to its influence and the results obtained from the cork phantom study (Fig. 2) suggest that errors up to 10% for the strip middle and 15% for the strip end could be encountered when measuring a lung density of 0.3 g cm^{-3} . While we have not attempted to compare these values to the theoretical background obtained by convolving the appropriate point spread function with simulated scan data for a "hollow" water phantom, we believe that the value of 10% measured at the centre of the phantom is higher than would be expected by virtue of simple resolution effects alone and that there may be other sources of error. However, the errors obtained in these phantom studies probably represent a worst case for measurements in man because of the modest size of the cork block ($14 \times 8 \text{ cm}$), the quantity of water surrounding the block, and the fact that, in the lung analysis, the ends of

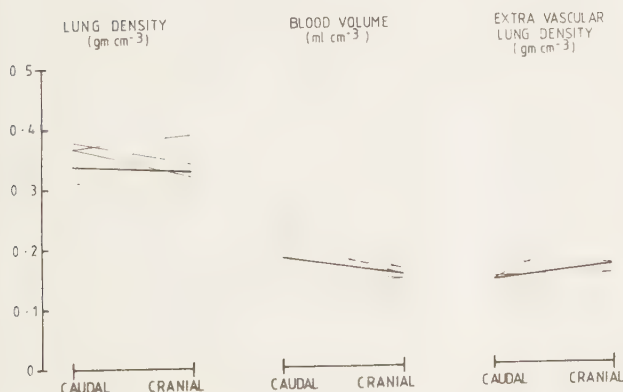


FIG. 5. Values of lung density, blood density, and extravascular lung density, taken from the caudal and cranial plane scans of five normal subjects (thin continuous lines have been used to join paired data points—mean values are denoted by the heavy line). An elliptical region of interest was chosen in each plane at the same gravitational level—midway between the heart and the chest wall.

the rectangular region of interest invariably meet the chest wall at an angle (in the plane of the scan) and are effectively some distance away from it.

Finally, it should be noted that the validity of the blood volume scan is dependent on there being no areas of haemostasis in the lung, which, if present, would result in local increases in the ^{11}C -carboxyhaemoglobin concentration (because of trapped, labelled red cells) with the consequent invalidation of the blood volume measurement within those regions. Although the inhalation of carbon monoxide (labelled with either ^{11}C or ^{15}O) has been used qualitatively for the detection of pulmonary haemorrhage (19) and pulmonary ischaemic lesions (20), it is doubtful whether this trapping effect would occur outside well defined patient groups. Patients within these groups could still be studied if the blood label was introduced intravenously, either as red blood cells labelled with ^{11}CO or as transferrin labelled with ^{67}Ga .

Lung Density Measurements

The measured anteroposterior gradient in the distribution of lung density was broadly predictable from earlier work on the gravitational dependence of various haemodynamic parameters in the lung (21–24) and from the later results of CT (3), which show a gravitationally dependent gradient in density. The fact that the density gradient falls appreciably with the subtraction of the vascular component is, therefore, not surprising. The slight residual gradient in the distribution of extravascular lung density is probably an indication of the different degree of lung expansion in the vertical direction by virtue of the lung weight (25).

The caudal-cranial differences in the vascular and extravascular lung density of isogravitational lung regions is small in this group of normal subjects, with vascular and extravascular compartments contributing almost equally to lung density. However, this pattern may change substantially in certain pathological conditions (pulmonary oedema, vascular congestion, emphysema, or sarcoidosis, for example) where, in particular, the extravascular:vascular density ratio could prove to be a sensitive index of abnormality. Using indicator dilution techniques to measure regional lung water, Fazio et al. (11) obtained a similar distribution of extravascular lung water per unit blood volume between caudal and cranial regions in the supine normal man. However, their values of this index (mean, 0.38 ± 0.11) are substantially less than would be predicted from our values of lung density, which result in an extravascular lung density:blood volume ratio of 0.90 ± 0.25 . Part of this difference may be attributable to the fact that in their technique the extravascular lung water is normalised to a blood

volume that almost certainly contains a blood volume component arising from the transit of indicator through the right heart and pulmonary artery and is, therefore, artificially high. In contrast, measurements made on the isolated perfused canine lung (24) using H_2^{15}O and ^{11}CO labelled red cells as diffusible and nondiffusible tracers suggest an almost equal contribution from vascular and extravascular water compartments to the total lung water.

To date, quantitative measurements of lung density, per se, have been confined to Compton scatter techniques that naturally include the vascular component. Values obtained in seated normal subjects by Gamsu et al. (26) ranged from 0.21 to 0.31 g cm^{-3} , with a mean of 0.26 g cm^{-3} , while Garnett and co-workers (7) obtained slightly higher values that ranged from 0.25 to 0.37 g cm^{-3} and had a mean of 0.32 g cm^{-3} . Although the values of lung density obtained in this study for the lower lung region from subject to subject (mean, -0.29 g cm^{-3} ; range, 0.26 to 0.32 g cm^{-3}) compare well with these published values, the range obtained for the individual regions in this plane (0.16 to 0.42 g cm^{-3}) is substantially greater. This difference undoubtedly results from the higher spatial sampling rate of this technique and reflects the true range of lung density values present in the plane.

While measurements of lung density have been made using CT, the results have been expressed in secondary units (Hounsfield or EMI numbers) and, to our knowledge, no density calibrations have been made in the range 0 to 0.75 g cm^{-3} . In a recent report on the *in vitro* calibration of these scanners at higher density values (14), an accuracy of 0.5% was predicted for soft tissue density measurements *in vivo*. However, this figure may be somewhat optimistic for measurements in the chest where bone:air interfaces may increase the problems of beam hardening, and breath-holding may well affect the regional blood content. In practice, variations in density arising from respiratory movements and uncertainties in the degree of lung inflation will probably be the limiting factors in the accuracy and reproducibility attainable both with CT and positron emission and transmission tomography.

In summary, we present a technique that provides accurate tomographic images of the distribution of both vascular and extravascular lung density. The ability to quantitatively differentiate between vascular and extravascular compartments will, we believe, help to give a better understanding of primary and secondary lung disease, especially when either compartment changes independently or at the expense of the other. The technique, which is now being used clinically to study a variety of lung diseases, requires a minimum of assumptions, is simple, noninvasive, nontraumatic, and requires little patient cooperation.

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Regional extravascular lung density and fractional pulmonary blood volume in patients with chronic pulmonary venous hypertension

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Summary. Using a technique based on positron transmission and emission tomography, we measured regional extravascular lung density (lung tissue and interstitial water per unit thoracic volume) and fractional pulmonary blood volume (volume of blood per unit thoracic volume) in normal subjects and in patients with cardiomyopathy and chronic pulmonary venous hypertension.

We found an increase in extravascular lung density in the patients. Extravascular density was increased in all parts of the lung studied, but higher values were seen in the dorsocaudal portion than in the ventrocaudal portion of the lung (average 151% and 130% of normal, respectively). Fractional blood volume was markedly reduced in the dorsocaudal part of the lung (mean 74% of normal).

The increase in extravascular density probably reflects structural changes in the lung as well as accumulation of interstitial fluid. The distribution of extravascular density is consistent with previous radiological and morphological studies, and may reflect a higher tendency to oedema formation in the dependent parts of the lung. The measurements of fractional blood volume suggest that intrapulmonary blood volume is reduced in chronic pulmonary venous hypertension. This may reflect a decrease in the distensibility of the pulmonary vessels due to structural abnormalities, as well as functional changes in the pulmonary vasculature.

Introduction

Heart diseases which cause longstanding pulmonary venous hypertension are accompanied by chronic interstitial pulmonary oedema. The increase in the size of the extravascular water pool in the lung in this condition has been well documented (Lilienfield *et al.*, 1955; Ramsey *et al.*, 1964; McCredie, 1967; Luepker *et al.*, 1971;

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O'Connor *et al.*, 1971; Fazio & Giuntini, 1979). Theoretical considerations (Staub, 1980), as well as radiological evidence (Fleischner & Reiner, 1954), indicate that the regional distribution of chronic interstitial oedema is not uniform, but little quantitative information has been obtained in man (Fazio *et al.*, 1976).

There has also been considerable interest in the pulmonary blood volume in chronic pulmonary venous hypertension. Even disregarding the measurements of 'central blood volume', which includes blood in the left heart chambers, the results of the measurements of the intravascular water pool are divergent. Some investigators have found an increased pulmonary blood volume (Fujimoto *et al.*, 1960; Dock *et al.*, 1961; Giuntini *et al.*, 1963; McGaff *et al.*, 1963; de Freitas *et al.*, 1964; Levinson *et al.*, 1964; Roy *et al.*, 1965), whereas others report insignificant changes (Varnauskas *et al.*, 1963; Schreiner *et al.*, 1966; Luepker *et al.*, 1971; Peräsalo & Heiskanen, 1971). Apart from radiological assessments, little information is available about the regional distribution of blood volume in the lung with chronic venous hypertension.

In this paper, we present regional measurements of extravascular lung density (i.e. the amount of lung tissue and interstitial fluid per unit thoracic volume) and fractional blood volume (volume of blood per unit thoracic volume) in patients with cardiomyopathy and chronic pulmonary venous hypertension. The observations were made using a recently described technique, based on positron tomography (Rhodes *et al.*, 1981).

Methods

The technique for measuring regional extravascular lung density and fractional blood volume with positron tomography has been described in detail elsewhere (Rhodes *et al.*, 1981) and only a short summary is therefore presented. Positron tomography is based on coincidence detection of the pair of γ -rays originating from the annihilation of a positron. In the instrument we used (ECAT II, EG & G ORTEC), detectors are placed in a hexagonal array around the patient. Annihilation events are recorded between pairs of detectors on opposite sides of the patient. The information is fed to a computer and subsequently used to reconstruct a transverse plane through the object in a way similar to that used in X-ray computed tomography.

In each study, two measurements were made with the patient in the supine position. For the first, an external ring source containing positron emitting isotope ($^{68}\text{Ge}/^{68}\text{Ga}$) was placed between the patient and the array of detectors. Following data collection and reconstruction, a transmission tomogram was thus obtained (Fig. 1, top left panel), showing the regional distribution of densities in a transversal plane through the chest. Due to the monochromatic nature and the high energy (511 keV) of the γ -photons, the count density in the lung in this tomogram is directly proportional to the physical density of the lung (g lung/ml thoracic volume) (Rhodes *et al.*, 1981). Transmission tomograms were obtained at two levels of the chest, at approximately the sternal insertion of the fourth rib and 8.5 cm in cranial direction.

Following this measurement, the patient inhaled a quantity of ^{13}C -carbon monoxide



Fig. 1. Tomograms of lung density (upper left panel), fractional blood volume (upper right panel) and extravascular lung density (lower panel) obtained at the level of the sternal insertion of the fourth rib in a supine normal subject

in order to label the blood pool. After the inhalation, 5 min were allowed for mixing before two emission tomograms were obtained in the same planes. This measurement showed the tomographic distribution of the isotope, i.e. the distribution of blood volume (Fig. 1, top right panel). The count density obtained in this case, together with a calibration of the tomograph, provided a quantitative measurement of the regional concentration of the isotope (Phelps, 1977).

The measurements thus yield quantitative information about the regional density of the lung and the fractional blood volume. Both measurements can be expressed in g/ml of thoracic volume, and therefore the contribution of blood to the measurement of the lung density subtracted to give a measurement of the extravascular density of the lung (lung tissue and interstitial water per unit thoracic volume; Fig. 1, bottom panel).

The radiation dose was less than one rad to the blood (critical organ). The investigation was approved by the Research Ethics Committee at the Royal Postgraduate Medical School and informed written consent was given by each patient.

DATA ANALYSIS

The tomograms constitute quantitative maps of the regional distribution of densities and fractional blood volume in the lung. Values for density and blood volume were obtained as mean picture element counts in a region of the lung. The ventrodorsal differences (vertical in the supine subject) were analyzed in a 1.7 cm wide region of interest, extending from the anterior to the posterior chest wall in the right lung field in the

caudal plane (Fig. 5, inset). The length of the region was normalised to 10 to allow for differences in size of the lung. The extreme parts of the region, points 1 and 10, were influenced by spillover from the chest wall (partial volume effect; Hoffman *et al.*, 1979) and were disregarded. The changes in ventrodorsal distribution of lung density and fractional blood volume were also expressed as the ratio between the ventral half of the region (segments 2 to 5) and the dorsal half (segments 6 to 9). The cranial and caudal parts of the lung were compared by selecting regions of equal size in the middle of the right lung field in each plane at the same gravitational level.

For comparison between lung densities and the functional status of the patient as well as intravascular pressure, it was desirable to measure the density in a large portion of the lung. Due to the limited spatial resolution of the positron tomograph (16 mm full width at half maximum), there is a gradual change in density between the lungs and the surrounding denser structures, and it is impossible to identify a distinct border of the lungs. We therefore used a thresholding programme, whereby the computer introduced an arbitrary demarcation of the lung at a density of 0.85 g/cc. This yielded tomograms of the two lungs (Fig. 2, inset), from which the mean densities and mean fractional blood volume could be measured. The mean density measured in this way was affected by spillover (partial volume effect; Hoffman *et al.*, 1979) from the chest wall and the heart. The partial volume effect was greater, the smaller the size of the lung field as is demonstrated in Fig. 2, where the mean densities measured in the lung fields of 19 normal subjects (38 lung fields) have been plotted versus the size of each lung field. The slope of the lines represents the partial volume effect, and the deviation from the regression lines reflects methodological errors as well as interindividual variation in lung density and variation in the shape of individual lung fields.

The equations for the regression lines shown in Fig. 2 were used to calculate a predicted value for the density and blood volume in each lung in the patients. The measurements were then expressed as % of predicted value and the mean value for the left and right lung used for comparisons with the clinical status of the patient and left ventricular end diastolic pressure. In four cases, the size of the left lung field fell below the range observed in normal subjects, in which case it was omitted.

Student's *t*-test was used for statistical analysis.

NORMAL SUBJECTS

We studied 19 normal subjects, 17 men and two women, in order to obtain reference values for lung densities. The group comprised six smokers and 13 non-smokers. There were no ex-smokers. The mean age was 35 years (range 20–56).

PATIENTS

Eight patients with cardiomyopathy, two smokers, two ex-smokers and four non-smokers, were studied (Table 1). All patients had been followed for at least 5 years and

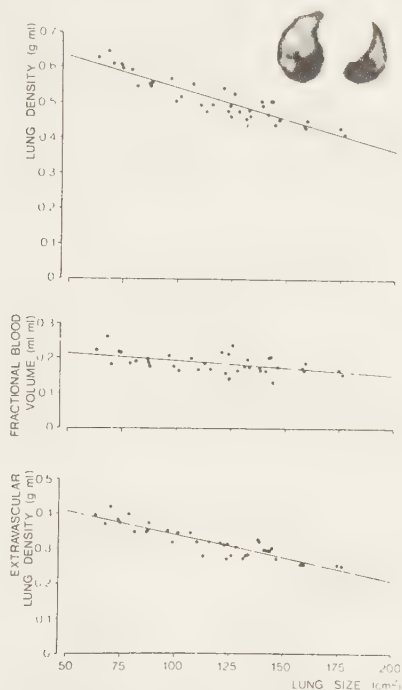


Fig. 2. Mean lung density, fractional blood volume and extravascular lung density as a function of lung field size in the lung fields of the caudal plane in nineteen normal subjects. The equations for the regression lines (continuous lines) were used to obtain predicted values for patients. Interrupted lines show 95% confidence limits. Inset: the lung fields were defined by a thresholding procedure and the mean value of density in this area calculated.

Table 1. Details of patients studied

Patient	Sex	Age (years)	Diagnosis	Functional class (NYHA)	LVEDP (mmHg)
1	M	32	HCM	I	10
2	F	34	HCM	I	—
3	M	40	CCM	II A	20
4	F	38	HCM	II A	20
5	M	57	HCM	II B	15
6	F	60	HCM	II B	30
7	M	34	CCM	III	24
8	F	41	HCM	III	35

HCM = hypertrophic cardiomyopathy; CCM = congestive cardiomyopathy.

were clinically and radiologically in stable condition. No patient had any history of primary lung disease. Functionally, the patients were in grade I–III of dyspnoea according to the classification of the New York Heart Association. Seven patients underwent left heart catheterization within 4 months of the study. The measured left ventricular end diastolic ranged from 10 to 35 mmHg. One patient refused catheterization. By clinical and radiological estimate, she had only slight elevation of the pulmonary venous pressure. Standard chest radiographs were obtained on the same day as the tomographic study.

Results

Tomograms of lung density, fractional blood volume and extravascular lung density obtained at the level of the sternal insertion of the fourth rib in a normal subject are shown in Fig. 1. As previously described with this technique (Rhodes *et al.*, 1981) as well as with X-ray computed tomography (Wegener *et al.*, 1978; Robinson & Kreel, 1979), there is a progressive increase in lung density from front to back in a supine subject (Fig. 1, top left panel). This is largely due to differences in blood content between the anterior and posterior part of the lung (Fig. 1, top right panel), the regional



Fig 3. Chest radiograph of patient number eight. A few septal lines can be seen at the lung bases.

differences in extravascular lung density being rather small (Fig. 1, bottom panel). In our population of normal subjects, we have not been able to demonstrate any relationship between lung density or fractional blood volume and sex, age or smoking habits.

The chest radiograph and tomograms of lung density, fractional blood volume and extravascular lung density of patient number eight are shown in Fig. 3 and 4. The chest radiograph in this patient (Fig. 3) showed a few horizontal lines at the lung bases compatible with chronic interstitial oedema. The regional distribution of lung density (Fig. 4, top left panel) was similar to that seen in normal subjects. The regional blood volume, however, was markedly abnormal (Fig. 4, top right panel). Instead of the normal ventrodorsal gradient of blood volume, there was an almost uniform distribution throughout the lung field. The extravascular lung density (Fig. 4, bottom panel) was increased in the patient, the increase being greater in the dorsal part of the lung than in the ventral part, resulting in an abnormal front-to-back difference.

Fig. 5 shows the ventrodorsal distribution of densities in the right lung for all eight patients compared to that in the normal subjects. Lung density (top panel) in the patients shows only minor deviations from normal. Fractional blood volume (middle panel) is normal in the ventral part of the lung but in most patients reduced to about half in the dorsal part of the lung. Instead of the normal front-to-back gradient of blood volume, these patients show a rather flat distribution. Two patients follow the normal pattern—these are patient number one, with normal left ventricular end diastolic pressure, and patient number two, who refused catheterization. Extravascular lung



Fig. 4. Tomograms of lung density (upper left panel), fractional blood volume (upper right panel) and extravascular lung density (lower panel) in patient number eight. Fractional blood volume is reduced and the normal ventrodorsal gradient is absent. Extravascular lung density is increased, especially in the dorsal part of the lung. The left lung (right in the image) was omitted from the analysis since the cross-sectional area was very small and heavily affected by the partial volume effect.

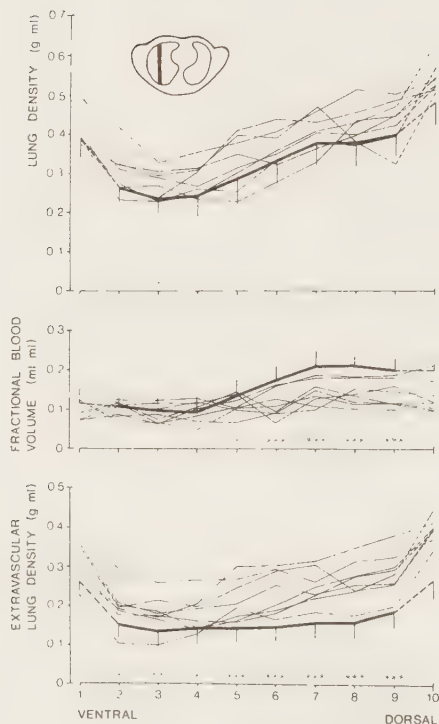


Fig. 5. Ventrodorsal profiles of lung density, fractional blood volume and extravascular lung density. A 1.7 cm wide region was chosen in the middle of the right lung (inset). Thick lines denote mean of 19 normal subjects and vertical bars one SD. Thin lines represent individual patients. Points 1 and 10 are influenced by 'spillover' from the chest wall. Asterisks denote significant deviations from normal: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

density (bottom panel) is significantly increased throughout the lung region in most patients. The increase is greater in the posterior part of the lung (mean 0.28 g/ml or 151% of normal) than in the anterior part (mean 0.19 g/ml or 130% of normal). Deflation of the lung (decrease in fractional residual capacity) would cause an increase in extravascular lung density. In order to assess the importance of this mechanism, we have normalized extravascular lung density to fractional blood volume (Fazio *et al.*, 1976; Hales *et al.*, 1981). The ventrodorsal distribution of the normalized extravascular lung density is shown in Fig. 6. In normal subjects, the ratio is higher in the anterior part

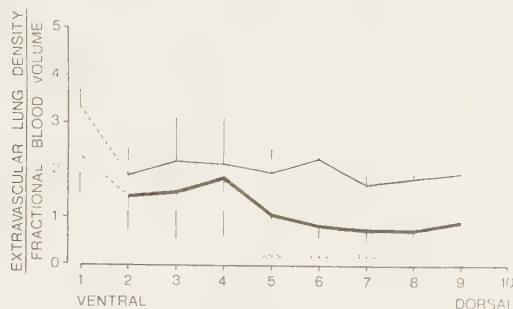


Fig. 6. Ventrodorsal profiles of extravascular lung density after normalization to fractional blood volume. Thick line shows mean of normal subjects and thin line mean of the patients. Vertical bars show one SD. Other symbols as in Fig. 5.

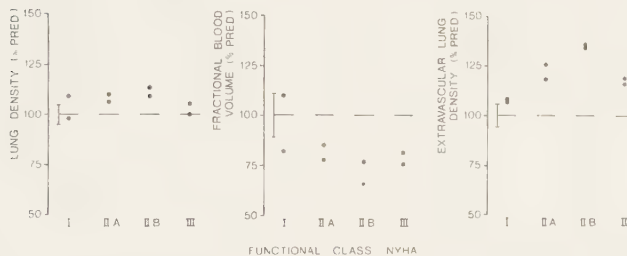


Fig. 7. Relation between lung densities and functional status of the patient. Horizontal lines show the normal value and vertical bars one SD.

of the lung than in the posterior. In the patients, the increase in extravascular lung density relative to blood volume is greater in the dorsal than in the ventral part of the lung.

In Table 2, the redistribution of lung density and blood volume is presented as the ratio between the ventral half of the region and the dorsal half. The increase in extravascular lung density and the reduction in fractional blood volume is greater in the dorsal part of the lung.

Table 3 presents the difference in densities and blood volume between the plane at the level of the sternal insertion of the fourth rib (caudal) and the plane 8.5 cm in the

Table 2. Difference in lung density and blood volume between non-dependent and dependent parts of the lung

		Ratio non-dependent to dependent lung			
		LD	FBV	ELD	ELD/FBV
Patients	Mean	0.73	0.73*	0.75 [‡]	1.09*
	SD	0.08	0.17	0.08	0.29
Normals (<i>n</i> = 19)	Mean	0.69	0.55	0.87	1.79
	SD	0.07	0.08	0.10	0.40

LD = lung density; FBV = fractional blood volume; ELD = extravascular lung density.

P* < 0.001; [‡]*P* < 0.01 (significant deviations from normal).Table 3.** Difference in lung density and blood volume between caudal and cranial parts of the lung at the same gravitational level

Patient	Caudal plane				Cranial plane			
	LD (g/ml)	FBV (ml/ml)	ELD (g/ml)	ELD/FBV (g/g)	LD (g/ml)	FBV (ml/ml)	ELD (g/ml)	ELD/FBV (g/g)
1	0.38	0.19	0.19	0.95	0.37	0.19	0.20	1.14
2	0.38	0.18	0.20	1.07	0.35	0.16	0.18	1.04
3	0.51	0.20	0.31	1.50	0.36	0.12	0.24	1.99
4	0.35	0.11	0.24	2.15	0.38	0.14	0.23	1.62
5	0.32	0.10	0.22	2.09	0.32	0.11	0.21	1.89
6	0.42	0.11	0.31	2.80	0.34	0.09	0.24	2.47
7	0.44	0.14	0.28	1.90	0.50	0.18	0.31	1.60
8	0.36	0.12	0.23	1.75	0.32	0.07	0.25	3.41
Mean	0.40*	0.14*	0.25 [‡]	1.78 [‡]	0.37	0.13	0.23 [‡]	1.90 [‡]
SD	0.06	0.04	0.05	0.60	0.05	0.04	0.04	0.76
Normals (<i>n</i> = 19)								
Mean	0.34	0.18	0.15	0.82	0.32	0.15	0.16	1.04
SD	0.05	0.04	0.04	0.30	0.05	0.02	0.04	0.34

LD = lung density; FBV = fractional blood volume; ELD = extravascular lung density.

**P* < 0.05; [‡]*P* < 0.01; [‡]*P* < 0.001 (significant deviations from normal).

cranial direction. Lung density is slightly increased, but this is statistically significant only in the caudal plane. Fractional blood volume is reduced, but again statistical significance is reached only in the caudal plane. Extravascular lung density, however, is increased at both levels, but more in the caudal portion of the lung than in the cranial (164% of normal compared to 141% of normal). When extravascular lung density is normalized to blood volume in a way similar to that suggested by Fazio *et al.* (1976), the increase in this ratio is greater in the basal part than in the apical part of the lung.

A comparison was made between the mean density seen in the caudal plane and the

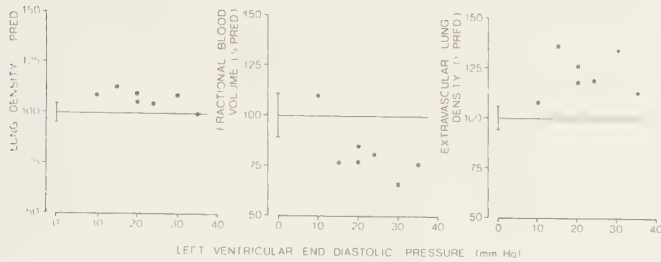


Fig. 8. Relation between lung densities and left ventricular end diastolic pressure. Horizontal lines show the normal value and vertical bars one SD.

functional status of the patient as well as the left ventricular and diastolic pressure. Fig. 7 relates the mean densities to the functional status of the patients. There is no consistent change in lung density with functional changes, but there is a tendency for the fractional blood volume to decrease and the extravascular lung density to increase with functional deterioration. Fig. 8 shows mean densities versus left ventricular end diastolic pressure. Changes in lung density are small, but there is a tendency for the fractional blood volume to decrease with increasing pressure. The values for extravascular lung density are too scattered to show any reliable trend.

Discussion

Chronic pulmonary venous hypertension secondary to heart disease is associated with a variety of structural and functional abnormalities in the lung. Most of the available information about extravascular water pool size has been obtained using indicator dilution techniques. Although it is generally accepted that these techniques underestimate extravascular water (Staub, 1974; Giuntini & Fazio, 1979), most studies have shown consistent increases in extravascular water in the order of 50–100% (Lilienfield *et al.*, 1955; Ramsey *et al.*, 1964; McCredie, 1967; Luepker *et al.*, 1971; O'Connor *et al.*, 1971; Pistolesi & Giuntini, 1978; Fazio & Giuntini, 1979). In recent years, there has been considerable interest in the regional distribution of extravascular lung water. Most of the information has been obtained from animal models (Staub *et al.*, 1967; Naimark *et al.*, 1971; Jones *et al.*, 1976; Baile *et al.*, 1979; Flick *et al.*, 1979; Ahluwalia *et al.*, 1981; Hales *et al.*, 1981; Huchon *et al.*, 1981), either under base-line conditions or in acutely induced oedema. Only one study reports quantitative data about the regional distribution of extravascular lung water in man (Fazio *et al.*, 1976).

Pulmonary blood volume has been extensively studied in pulmonary venous hypertension using indicator dilution techniques. The results obtained range from substantial

increases to insignificant changes in pulmonary blood volume in chronic pulmonary venous hypertension.

The aim of the present study was to measure regional changes in the extra- and intravascular compartments in patients with pulmonary venous hypertension. We have used a recently developed tomographic technique (Rhodes *et al.*, 1981) which provides accurate measurements of the extravascular density of the lung (g lung tissue plus interstitial water/ml thoracic volume) and the fractional pulmonary blood volume (g/ml thoracic volume or ml/ml thoracic volume). A limiting factor of the method is the influence of the surrounding chest wall and heart on the measurements of lung density and fractional blood volume. This problem is inherent in the tomographic technique and leads to inaccuracies in the measurements at the periphery of the lung (Rhodes *et al.*, 1981). Therefore, in the analysis of ventrodorsal (Fig. 5, 6) and craniocaudal (Table 3) differences in the lung, we have omitted the peripheral parts of the lung (Rhodes *et al.*, 1981). For a comparison with other functional parameters (Fig. 7, 8), it was desirable to use large portion of the lung. For this reason, a correction for the influence of the surrounding structures was introduced (Fig. 2). Results similar to those presented in Figs. 7 and 8 were obtained by selecting a small region of interest in the centre of the lung field. Apart from being representative for only a very small proportion of the lung, these results were dependent on the selection of the region and were not considered satisfactory.

We found increased extravascular lung density in both planes studies. This suggests that extravascular lung density was increased throughout the lung. There was also regional variation in extravascular lung density, the highest values being seen in the posterior part of the caudal plane. When levels at the same height in the caudal and cranial planes were compared, the increase in extravascular lung density was greater in the caudal part of the lung (164% of normal) than in the cranial part (141%). Deflation of the lung causes an increase in lung density (Robinson & Kreel, 1979) and the increase we found in extravascular lung density could at least in part be explained by a reduction in functional residual capacity in the patients. The ratio between extra- and intravascular density can be expected to be much less dependent on lung volume. The ratio between extra- and intravascular fluid volume has also been used by other authors as a measure of pulmonary oedema (Fazio *et al.*, 1976; Hales *et al.*, 1981). After normalization to fractional blood volume, extravascular lung density was still increased in the patients, and the pattern of changes was similar, i.e. the increase was greatest in the dependent parts of the lung. We therefore do not think that reduced lung inflation gives an important contribution to our findings. When extravascular lung density was normalized to blood volume in the caudal and cranial plane, the ratios were 217% and 182% of normal, respectively. These results are very similar to those obtained by Fazio *et al.* (1976), i.e. 203% at the base of the lung and 168% at the apex.

The precise nature of the changes in the lungs is not clear from the measurement since we can not distinguish between tissue and free interstitial water. The structural changes occurring in the lung in chronic pulmonary venous hypertension are well

described (Parker & Weiss, 1936; Doyle *et al.*, 1957; Heath & Edwards, 1959). Thickening of the vessel walls occurs as well as interstitial fibrosis. These changes are often more pronounced in the lower lobes, which suggests that structural changes may represent part of the increase in extravascular lung density.

It has often been suggested that oedema formation should be greater in the dependent part of the lung, since there is an intravascular pressure gradient due to the height of the lung that may not be balanced by a corresponding gradient in perivascular pressure. In ambulant patients, the highest degree of oedema formation could therefore be expected to occur in the caudal and dorsal parts of the lung. This may be reflected in the regional distribution of structural changes in the lung parenchyma and in the distribution of extravascular lung density.

There was a tendency for the extravascular lung density to increase with the disability of the patient (Fig. 7). This is consistent with the results reported by Ramsey *et al.* (1964), McCredie (1967), Luepker *et al.* (1971) and Yu (1971). Staub (1974) combined the results of Ramsey *et al.*, McCredie and Luepker *et al.* and showed a considerable overlap in the lung water measurements in the different classes. When compared to left ventricular end diastolic pressure, the values for extravascular lung density were rather scattered. Linear relations between left atrial pressure and extravascular lung water, measured with indicator dilution technique, have been reported by McCredie (1967), Luepker *et al.* (1971), Yu (1971) and O'Connor *et al.* (1971). The scatter has been considerable in these studies and a correlation could hardly be expected from our study.

The fractional blood volume was reduced in the dorsocaudal part but normal in the ventrocaudal part of the lung in our patients. In the patients with substantial venous hypertension, the gravity-dependent gradient of blood volume was absent. In the cranial plane, fractional blood volume was reduced in some patients, but the mean value was not significantly different from normal. There was also a tendency for fractional blood volume to decrease with disability and increasing intravascular pressure. The results imply that the intrapulmonary blood volume is reduced in chronic pulmonary venous hypertension. Although we did not see any signs of recruitment of vascular beds in terms of absolute increases in regional blood volume, there was a relative redistribution of blood away from the dependent parts of the lung. This pattern is similar to that often seen in chest radiographs, and also to the pattern of regional perfusion seen in pulmonary venous hypertension (Dollery & West, 1960; Dawson *et al.*, 1965; Friedman & Braunwald, 1966; Giuntini *et al.*, 1974).

Most previous studies have shown the pulmonary blood volume to be increased in chronic pulmonary venous hypertension (Fujimoto *et al.*, 1960; Dock *et al.*, 1961; McGaff *et al.*, 1963; de Freitas *et al.*, 1964; Levinson *et al.*, 1964; Roy *et al.*, 1965), whereas others show insignificant changes compared to normal (Varnauskas *et al.*, 1963; Schreiner *et al.*, 1966; Luepker *et al.*, 1971; Peräsalo & Heiskanen, 1971). This apparent discrepancy between our results and the previous measurements can be explained by the fact that the different techniques measure different parts of the

vascular bed. Indicator dilution techniques, which employ injections of indicator into the pulmonary artery and the left atrium and sample from a systemic artery (Fujimoto *et al.*, 1963) measure the blood volume between the pulmonary valve and the left atrium. A similar volume is measured by external monitoring of a radioactive tracer (Giuntini *et al.*, 1963), whereas the technique used in this study measures the volume of blood in the intrapulmonary vessels alone. Although the blood volume in the pulmonary circulation as a whole is normal or increased, the volume in extra- and intrapulmonary vessels may change in opposite directions. Dock *et al.* (1961) and McGaff *et al.* (1963) studied patients with mitral stenosis and found increasing blood volume with increasing left atrial pressure except in patients with high pulmonary vascular resistance, who had a smaller blood volume relative to the intravascular pressure. McGaff *et al.* suggested that this was due to widespread decrease in pulmonary vascular distensibility in patients with high resistance. Schreiner *et al.* (1966) and Yu (1971) have put forward a similar explanation for their findings of normal pulmonary blood volume in functionally severely limited patients with pulmonary venous hypertension. Doyle *et al.* (1957) performed post-mortem angiography on lungs from patients with pulmonary venous hypertension due to mitral stenosis. They were able to demonstrate enlargement of the main pulmonary artery in a large proportion of these cases. The caliber of segmental and smaller arteries was reduced in the caudal part of the lung but normal in the cranial part. The findings are thus compatible with an increase in the volume of extrapulmonary blood volume. Doyle *et al.* also studied the structural changes in the pulmonary vasculature and found that the hypertrophy of the arterial and venous vessel walls was always greater in the caudal than in the cranial part of the lung.

We think that a reduced distensibility of the vessels due to structural changes and/or increased smooth muscle tone is a likely explanation for the reduction in intrapulmonary blood volume in our patients. A contributing factor could be an increase in perivascular pressure due to the accumulation of oedema fluid (West *et al.*, 1965; Hughes *et al.*, 1968). This mechanism seems, however, to require special conditions of low driving pressure and low flow (Ritchie *et al.*, 1969).

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III

REGIONAL EXTRAVASCULAR DENSITY AND FRACTIONAL BLOOD VOLUME OF THE LUNG IN INTERSTITIAL DISEASE

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ABSTRACT

With a technique based on positron tomography, regional lung density (g lung/ml thoracic volume) and fractional pulmonary blood volume (ml blood/ml thoracic volume) has been measured in ten patients with interstitial disease. From the measurements, regional extravascular lung density (g tissue and interstitial water/ml thoracic volume) was derived, providing a noninvasive measurement of the interstitial reaction. Extravascular lung density was increased and large regional variations were observed. Fractional blood volume was reduced in patients with pulmonary fibrosis. In two patients with sarcoidosis, a reduction in extravascular lung density occurred after treatment with oral prednisone. Abnormalities in extravascular lung density and fractional blood volume correlated with tests of overall pulmonary function.

INTRODUCTION

A technique for quantitative measurement of extravascular lung density (lung tissue and interstitial fluid per unit thoracic volume) and the fractional blood volume in the lung (volume of blood per unit thoracic volume) by means of positron tomography has recently been described (1). The purpose of this study was to evaluate the use of this technique for investigation of interstitial lung disease.

Interstitial diseases are characterized by chronic interstitial inflammation and derangement of alveolar structures (2). While some patients show spontaneous remissions, other progress to pulmonary fibrosis with permanent loss of lung function. Quantitative measurements of the disease process in the lung could be of value for monitoring the effect of therapy and are essential if the relation between interstitial reaction and pulmonary function is to be clarified.

MATERIAL AND METHODS

PATIENTS

Five patients with sarcoidosis having mild to moderate functional impairment (group 1) were studied. Details of the patients are presented in Table 1. In all five patients, a histological diagnosis had been made. Three of the patients were treated with prednisone (20 mg daily) for four to six weeks and subsequently restudied.

Five patients with severe functional impairment (group 2) were also studied. Three patients had end-stage disease, two from fibrosing alveolitis, the other from sarcoidosis. The other two patients in this group had presented with breathlessness. In both patients, crackles were found on physical examination and the chest radiographs showed basal nodular shadowing. Patient No. 9 had chronic hypoxaemia and finger

Table 1. Details of patients studied.

Patient	Sex	Age	Age at diagnosis	Radiological appearance	Histology
Group 1					
1	M	40	30	Widespread interstitial shadowing	Lung biopsy: NCG Kveim's reaction positive
2	M	29	28	Bilateral hilar lymphadenopathy	Lung biopsy: NCG
3	F	36	34	Bilateral hilar lymphadenopathy, widespread nodular shadowing	Lung biopsy: NCG
4	M	32	26	Bilateral hilar lymphadenopathy, widespread nodular shadowing	Lung biopsy: NCG
5	F	47	44	Perihilar and apical stippling	Lung and lymph node biopsy: NCG Kveim's reaction positive
Group 2					
6	M	65	65	Gross basal shadowing	Autopsy: Fibrosing alveolitis
7	M	66	46	Coarse reticular shadowing	Lung biopsy: Fibrosing alveolitis
8	M	41	31	Widespread interstitial shadowing	Lymph node biopsy: NCG Kveim's reaction positive
9	M	76	72	Basal nodular shadowing	None.
10	M	59	56	Basal nodular shadowing	Kveim's reaction negative
					None. Kveim's reaction negative

NCG = non-caseating granulomata

clubbing. A clinical diagnosis of pulmonary fibrosis had been made. Both patients slowly deteriorated during the period of observation.

The study was approved by the Research Ethics Committee of the Royal Postgraduate Medical School, and written informed consent was obtained from each patient.

PULMONARY FUNCTION TESTS

Standard pulmonary function tests were performed on the same day as the tomographic study. Vital capacity (VC) and forced expiratory volume ($FEV_{1.0}$) were recorded with a dry spirometer. Total lung capacity (TLC) was measured by body plethysmography. The single breath method was used for measuring the transfer factor for carbon monoxide (T_{LCO}). Predicted values were obtained from Quanjer (3) and from Bradley et al (4).

POSITRON TOMOGRAPHY

The technique for measuring regional extravascular lung density and fractional blood volume has previously been described in detail (1), and is only summarized here.

Positron tomography is based on coincidence detection of the pair of γ -rays originating from the annihilation of a positron. In the instrument we used (ECAT II, EG&G ORTEC), annihilation events are recorded between pairs of detectors placed in a hexagonal array around the supine patient. The information is fed to a computer and subsequently used to reconstruct a transverse plane through the object in a way similar to that used in X-ray computed tomography.

Protocol

In each study, two measurements were made with the patient in the supine position. The first measurement was made with an external ring source containing a positron-emitting isotope ($^{68}\text{Ge}/^{68}\text{Ga}$) placed between the

patient and the array of detectors. The transmission tomogram thus obtained (Fig. 1, top left panel) showed the distribution of density in the plane chosen and provided a quantitative measurement of the density of the lung (g lung/ml thoracic volume). Tomograms were obtained at two levels of the chest: one at approximately the sternal insertion of the fourth rib and the other 8.5 cm in the cranial direction.



Fig. 1. Tomograms of lung density [top left], fractional blood volume [top right] and extravascular lung density [bottom] from a normal subject.

Following this measurement, the patient inhaled a quantity of ^{11}C -carbon monoxide (^{11}CO) in order to label the blood pool. After the inhalation, five minutes were allowed for mixing before emission tomograms were obtained at the same two levels. During the measurement, venous blood was sampled and the concentration of ^{11}CO in peripheral blood subsequently measured in a well counter, cross calibrated with the ECAT. The emission tomogram showed the regional distribution of blood volume (Fig. 1, upper right panel). A quantitative measurement of the fractional blood volume in the lung (ml blood/ml thoracic volume) was obtained by dividing the regional concentration of ^{11}CO with the concentration in whole blood.

Data analysis

Since lung density and fractional blood volume can be expressed in the same units (g/ml thoracic volume), regional extravascular lung density (lung tissue and interstitial fluid per unit thoracic volume) can be calculated (Fig. 1, bottom panel) by subtraction.

The resolution in the reconstructed tomograms is 17 mm (measured as the full width at half maximum of the response to a line source of activity). Due to the limited resolution, there is a gradual change in the measured density from the chest wall to the lung. This means that it is impossible to identify a distinct border of the lung in the tomogram, and that the peripheral part of the lung is affected by "spillover" from the chest wall (partial volume effect; 5).

For comparison with lung function tests, extravascular lung density and fractional pulmonary blood volume were averaged over a large proportion of the lung by delineating the right and left lung fields in the caudal plane using a cut-off density value of 0.85 g/ml to define the edge of the lung. The mean density and fractional blood volume in this volume were related to predicted values obtained from normal subjects (6). Allowance for the partial volume effect was made by taking the size of the lung into account.

Regional variations in extravascular lung density and fractional blood volume were analysed in two ways. Ventrodorsal (vertical in the supine subject) differences were measured within a 17 mm wide strip through the right lung field in the caudal plane (Fig. 5, inset). This strip was divided into ten sections to account for differences in lung size. Sections one and ten were disregarded because of the influence of the chest wall. Craniocaudal differences were analyzed by selecting regions of interest of equal size in the middle of the right lung field at the same gravitational level.

The patients were compared to a reference group of 19 normal subjects (17 men and 2 women) (6) with a mean age of 35 years (range 20 to 56). Student's t-test was used for statistical analysis.

RESULTS

PULMONARY FUNCTION TESTS

Results of the lung function tests are presented in Table 2. In the majority of patients, a reduction in lung volumes and the transfer factor for carbon monoxide was found. Although there was considerable scatter, impairment of lung function tended to be worse in patients in group 2 than in group 1.

Table 2. Results of pulmonary function tests.

Patient	VC (% pred)	FEV1.0 (% pred)	TLC (% pred)	TLC0 (% pred)
Group 1				
1	86	58	97	77
2	86	80	87	75
3	85 (102)	89 (111)	106 (101)	55 (93)
4	96 (100)	98 (105)	95 (90)	82 (95)
5	60 (60)	62 (65)	60	54 (57)
Group 2				
6	74	65	-	29
7	44	50	-	-
8	55	50	76	12
9	105	87	96	32
10	72	23	109	71

Figures in brackets represent results obtained after treatment

TOMOGRAPHIC APPEARANCE AND RELATION TO CHEST RADIOGRAPH

Tomograms of lung density, fractional blood volume and extravascular lung density from a normal subject are shown in Fig. 1. In normal subjects, there is a ventrodorsal gradient of lung density (upper left panel), caused mainly by differences in fractional blood volume (upper right panel). Extravascular lung density (bottom panel) has a more uniform distribution (1).

Chest radiographs and tomograms from a patient with sarcoidosis (patient No. 3) are shown in Figures 2 and 3. In the pre-treatment radiograph (Fig. 2A), there was gross bilateral lymphadenopathy and extensive shadowing in the right lung. Lung density (Fig. 2B, upper left panel) was greatly increased in the right lung field. Fractional blood volume (upper right panel) was reduced in the dorsal part of the right lung field, corresponding to the right lower lobe. The increase in density was thus accounted for by abnormalities in the extravascular compartment (lower panel). Following treatment with prednisone (30 mg daily), there was a reduction in the radiographic abnormalities (Fig. 3A). Fractional blood volume (upper right panel) returned to normal and extravascular lung density (lower panel) was greatly reduced. Major regional abnormalities in fractional blood volume were not seen in any other patient in group 1.

The chest radiograph and illustrative tomograms of lung density, fractional blood volume and extravascular lung density from a patient in group 2 (No. 6) with idiopathic pulmonary fibrosis are shown in Fig. 4. Lung density (Fig. 4B, upper left panel) was increased in the patient due to an increase in extravascular lung density (lower panel). The abnormalities were greatest in the periphery of the lung. Fractional blood volume was reduced and showed an irregular pattern (upper right panel).

A



B

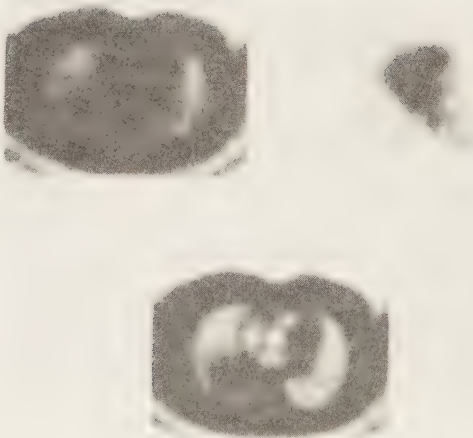


Fig. 2. Chest radiograph (A) and tomograms (B) from a patient with sarcoidosis. Lung density (top left) is increased due to an increase in extravascular lung density (bottom). Fractional blood volume (top right) is reduced in the dorsal part of the right lung field, corresponding to the lower lobe.

A



B



Fig. 3. Chest radiograph (A) and tomograms (B) from the patient in Fig. 2 after a period of steroid treatment. Improvement is seen in extravascular lung density (bottom) as well as in fractional blood volume (top right).

A



B

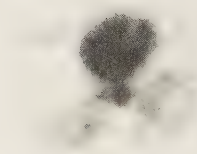
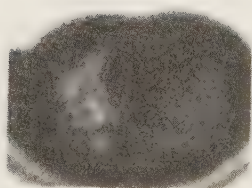


Fig. 4. Chest radiograph (A) and tomograms (B) from a patient with fibrosing alveolitis. Lung density (top left) and extravascular lung density (bottom) is increased, especially at the periphery of the lung. Fractional blood volume (top right) is reduced.

RELATION TO PULMONARY FUNCTION TESTS

Mean density and fractional blood volume throughout the lung fields for the caudal plane are presented in Table 3. A small but statistically significant increase in lung density was found in the patients in group 1. When the intra- and extravascular compartments were separated, the increase in lung density could be attributed to an increase in extravascular lung density, whereas fractional blood volume was not significantly different from normal. The ratio between extravascular lung density and fractional blood volume was greatly increased. In the patients in group 2, there was also a small increase in lung density. In this group, fractional blood volume was reduced in addition to the increase in extravascular lung density. The ratio between extravascular lung density and fractional blood volume was also increased.

In relation to pulmonary function tests, significant correlations were found between extravascular lung density and VC ($r = -0.56$, $p < 0.05$) as well as $FEV_{1.0}$ ($r = -0.62$, $p < 0.05$) when data from both groups were considered. The ratio between extravascular lung density and fractional blood volume also correlated with VC ($r = -0.56$, $p < 0.05$) and $FEV_{1.0}$ ($r = -0.70$, $p < 0.01$).

No correlation was found between the tomographic measurements and the T_{LCO} when data from both groups were considered. In group 1, however, a statistically significant correlation between mean fractional blood volume and the transfer factor for carbon monoxide was found ($r = 0.73$, $p < 0.05$) when both pre- and post-treatment measurements were considered. The ratio between extravascular lung density and fractional blood volume also correlated with the transfer factor in group 1 ($r = -0.83$, $p < 0.05$). No correlation was found in either instance for the patients in group 2. The diffusion constant for carbon monoxide did not correlate with the tomographic measurements.

Table 3. Mean lung density, fractional blood volume and extravascular lung density measured in the lung fields in the caudal plane.

Patient	LD (% pred)	FBV (% pred)	ELD (% pred)	ELD/FBV (% pred)
Group 1				
1	110	103	115	114
2	112	92	124	138
3	100 (100)	76 (98)	114 (101)	164 (107)
4	122 (114)	112 (122)	131 (108)	113 (85)
5	106 (102)	90 (89)	115 (111)	141 (137)
Mean	110**	95	120***	134***
SD	8	14	8	21
Group 2				
6	107	66	132	206
7	122	75	154	194
8	110	88	125	134
9	101	79	116	132
10	106	58	139	217
Mean	109**	73***	133***	177***
SD	8	12	14	41
Normal subjects (n=19)				
Mean	100	100	100	100
SD	4	11	6	13

LD = lung density

FBV = fractional blood volume

ELD = extravascular lung density

** p < 0.01, *** p < 0.001 (significant deviations from normal)

Figures in brackets represent results obtained after treatment.

RESPONSE TO STEROID TREATMENT

Of the three patients in group 1 who received steroid treatment, two (Nos. 3 and 4) showed a substantial reduction in extravascular lung density and some increase in fractional blood volume (Fig. 3B, Table 3). Patient No. 3 showed marked improvement in pulmonary function tests, while in patient No. 4, these changes were smaller. In the third treated patient, only minor improvement was seen in the tomographic measurements and the pulmonary function tests.

REGIONAL DIFFERENCES

The regional ventrodorsal distribution of lung density and fractional blood volume in normal subjects is characterized by a gradual increase in density and blood volume from the ventral to the dorsal part of the lungs (Fig. 5). The distribution of extravascular lung density is more uniform in the normal subjects. Most patients in group 1 showed a non-uniform increase in lung density and extravascular lung density, but no common pattern in the abnormalities could be identified. Three patients had a normal ventrodorsal distribution of fractional blood volume, whereas in the other two, blood volume was reduced in the dorsal part of the lung. In one of the latter patients (patient No. 3), the ventrodorsal distribution of blood volume returned to normal following steroid treatment (cf. Fig. 3B).

In some patients in group 2, lung density was lower than normal in the central part of the lung (Fig. 6). Fractional blood volume was reduced throughout the ventrodorsal region in most patients, and the ventrodorsal gradient was absent. There was a tendency for extravascular lung density to be lower in the central part of the ventrodorsal region than in the outer parts. (Note that the periphery of the lung is omitted from the analysis due to influence from the chest wall.)

The analysis of craniocaudal differences in lung density, fractional blood volume and extravascular lung density also revealed large regional variations, but there was no common pattern of abnormalities in any of the groups.

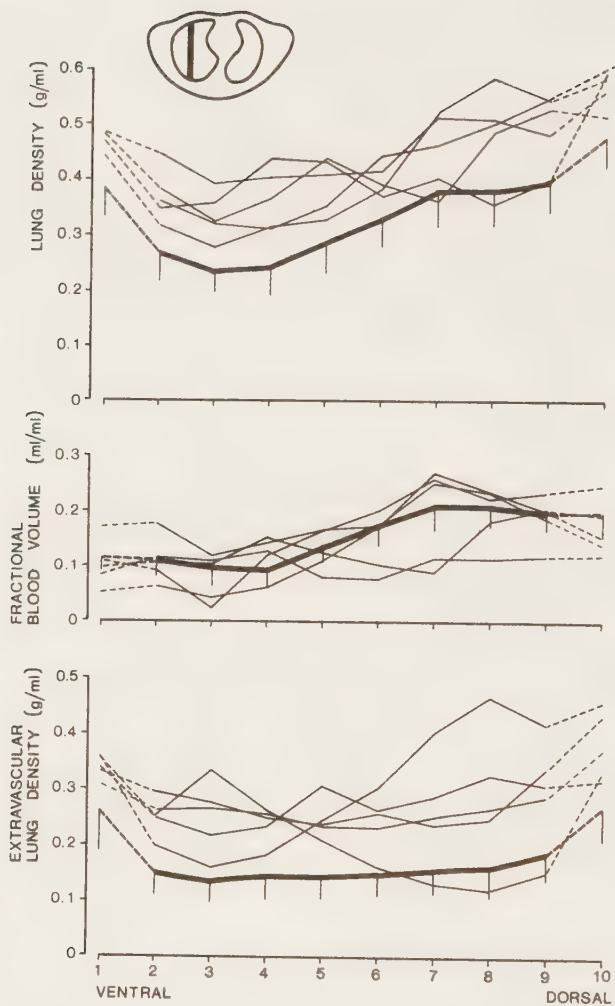


Fig. 5. Regional lung density, fractional blood volume and extravascular lung density in a ventrodorsal strip through the right lung (inset) in the patients in group 1. Thin lines represent individual patients. Thick line represents mean of 19 normal subjects and vertical bars one SD. Segments 1 and 10 are influenced by the chest wall.

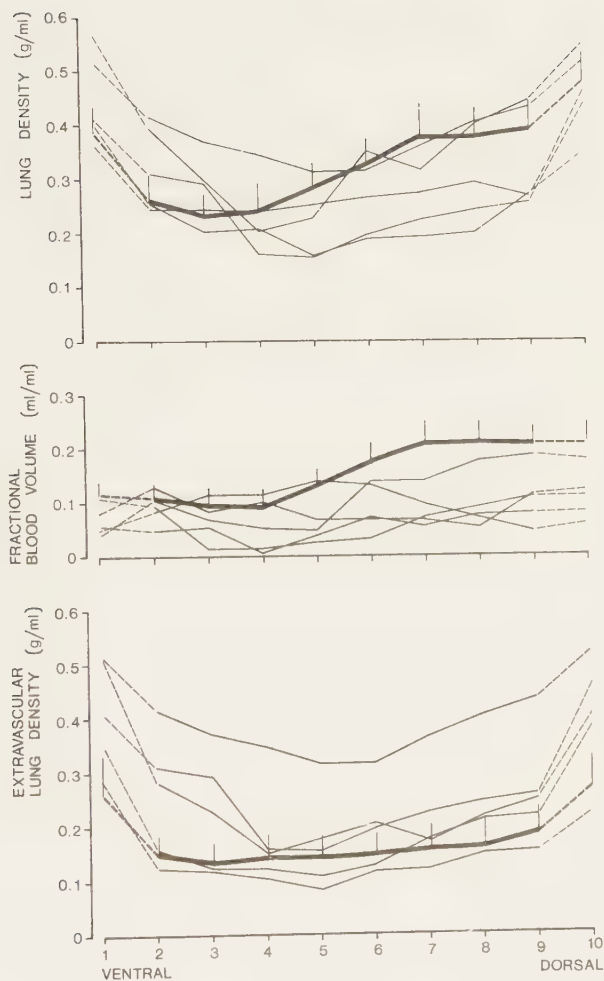


Fig. 6. Regional lung density, fractional blood volume and extravascular lung density in a ventrodorsal strip through the right lung in the patients in group 2. Symbols as in Fig. 5.

DISCUSSION

The many structural abnormalities occurring in interstitial lung disease include thickening of alveolar walls, interstitial inflammation with accumulation of inflammatory cells, formation of granuloma in sarcoidosis and eventually interstitial fibrosis (2). Of the numerous different techniques for evaluation of interstitial lung disease, only lung biopsy provides a complete picture of the interstitial reaction.

In this study, a technique (1) based on positron tomography was used to obtain measurements of extravascular lung density. This comprises lung tissue as well as interstitial water and accumulated inflammatory cells, and thus reflects all types of interstitial abnormalities in the lung. Differentiation between different causes for increased extravascular density requires the introduction of specific cellular or interstitial markers. Leucocytes have a high rate of glucose metabolism, and preliminary observations suggest that the pulmonary uptake of the glucose analogue ^{18}F -fluorodeoxyglucose can be used to measure white cell activity in the lung (Dr SO Valind, personal communication). The technique also provides a measurement of the fractional pulmonary blood volume. Only blood contained in intrapulmonary vessels (lobar vessels and smaller) is included in this measurement.

TECHNICAL ASPECTS

The tomographic measurements were made during tidal breathing in the supine posture. The acquisition time for the tomograms is five to ten minutes, and each measurement represents a large number of breathing and cardiac cycles. The partial volume effect introduces difficulties in the measurement of extravascular lung density and fractional blood volume in the peripheral part of the lung. When density and blood volume is averaged over the entire lung field, the whole transverse section of the lung is included in the measurement and allowance for the partial volume effect is made through the comparison with normal subjects (6). In the regional analysis, it is necessary to omit a section of the lung underlying the chest wall from the analysis.

Lung density, fractional blood volume and extravascular lung density are all affected by the degree of expansion of the lung, and the possibility that our results may in part be explained by a reduction in lung volume must be considered. A moderate reduction in lung inflation can be expected to be associated with increased fractional blood volume and extravascular lung density. However, the ratio between extravascular lung density and fractional blood volume would be less affected. In group 1, the reduction in lung volumes was small. Fractional blood volume was normal while extravascular lung density was increased. Modest reductions in lung inflation are unlikely to make major contributions to the increase in extravascular lung density. The finding of a substantial reduction in extravascular lung density in combination with small changes in lung volumes after treatment in patient number 4 also indicates that extravascular lung density is not heavily dependent on lung inflation. In group 2, there was greatly reduced fractional blood volume and increased extravascular lung density. This is unlikely to result from deflation of the lung per se.

MEASUREMENTS OF EXTRAVASCULAR LUNG DENSITY

Extravascular lung density averaged over the lung fields in the caudal plane was consistently increased in both groups of patients. The values tended to be higher in group 2 - patients with severe functional impairment - than in group 1, although the difference between the two groups of patients was not statistically significant. The reduction in extravascular lung density after steroid treatment in two patients with sarcoidosis was associated with improvement in radiological appearance and pulmonary function tests. This demonstrates the feasibility of measuring quantitatively and non-invasively the response to treatment in interstitial disease.

The regional analysis showed the distribution of interstitial abnormalities to be very non-uniform in patients in group 1. This is in keeping with previous radiological findings in patients with sarcoidosis (7).

The patients in group 2 also showed large regional variations in extravascular lung density. The lowest values were often seen in the centre of the lung field, which suggests a peripheral distribution of fibrosis (cf. Fig. 4B).

MEASUREMENTS OF FRACTIONAL BLOOD VOLUME

Only one patient with sarcoidosis of recent onset (patient No. 3, Fig. 2-3) showed a substantial reduction in fractional blood volume. This seemed to be confined to the right lower lobe and was reversible after steroid treatment. The reduction of fractional blood volume in this patient may be due to obstruction of hilar vessels by the enlarged hilar lymph nodes, as involvement of intraparenchymal vessels is likely to be irreversible.

All patients in group 2 had a reduced fractional blood volume, which may result from structural abnormalities involving the pulmonary vasculature. It is well established that capillary blood volume can be reduced in interstitial lung disease, especially in later stages (8-11). The magnitude of the abnormalities seen in this study suggests that larger vessels as well as capillaries are affected. This is supported by a post mortem arteriographic study (12), showing a reduced number of branches and diffuse narrowing of distal arteries in areas with severe fibrosis.

RELATION TO PULMONARY FUNCTION TESTS

Histological appearances correlate with reductions in VC in patients with sarcoidosis (13, 14) and other interstitial diseases (15). Similarly, we found a relatively weak correlation between VC and extravascular lung density. The transfer factor yields significant correlations with histological indices in sarcoidosis (13, 14, 16), but not in pulmonary fibrosis (17) or interstitial pneumonia (15). Correspondingly, fractional blood volume and the ratio between extravascular lung density and fractional blood volume correlated with T_{LCO} in patients with sarcoidosis but not in the fibrotic patients in group 2.

CONCLUSION

The study demonstrates the feasibility to measure non-invasively the structural abnormalities in the lung in interstitial disease and to monitor the effects of treatment.

In combination with tomographic techniques for measuring alveolar ventilation (18) or ventilation-perfusion ratios (19), the measurement of extravascular lung density could be useful for studies of the relationship between lung structure and function on a regional basis.

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IV

REGIONAL PULMONARY BLOOD VOLUME IN PATIENTS WITH ABNORMAL BLOOD PRESSURE OR FLOW IN THE PULMONARY CIRCULATION

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ABSTRACT

We studied the effects of chronic increase in flow and of chronic hypertension on regional pulmonary blood volume and extravascular lung density (lung tissue and interstitial water per unit thoracic volume) in one group of patients with intracardiac, left-to-right shunt and in one group with Eisenmenger's syndrome or primary pulmonary hypertension. We used positron computerized tomography to measure regional lung density (transmission scans) and blood volume (labelling with ^{11}CO).

The distribution of pulmonary blood volume was more uniform in patients with chronic increase in pulmonary blood flow than in normal subjects. There was also indications of an absolute increase in intrapulmonary blood volume. In patients with chronic pulmonary arterial hypertension, the regional distribution of blood volume was abnormally uniform, but there were no indications of substantial abnormalities in intrapulmonary blood volume.

The abnormally uniform distribution of pulmonary blood volume may be explained by recruitment or distension of vascular beds. The overall chronic degree of distensibility or recruitment of the intrapulmonary vasculature appears related to flow. Chronic hypertension is likely to be associated with reactive vascular changes preventing increase in intrapulmonary blood volume.

INTRODUCTION

The influence of vascular pressure on the regional distribution of pulmonary blood flow has been studied extensively both under experimental and clinical conditions (1). Little information is, however, available about the regional distribution of pulmonary blood volume in vivo, with the exception of the clinical radiological assessment.

We have used a tomographic technique, recently described by Rhodes et al (2) which provides regional, quantitative measurements of fractional pulmonary blood volume (volume of blood per unit thoracic volume), in order to study the effects of increased pulmonary flow and increased pressure on regional pulmonary blood volume in two groups of patients.

Since the technique also provides a measurement of regional extravascular lung density (lung tissue and interstitial water per unit thoracic volume), we were able to investigate the possible presence of interstitial tissue changes in the lung in patients with pulmonary hypertension.

MATERIAL AND METHODS

PATIENTS

We studied five patients with intracardiac left-to-right shunts, five patients with Eisenmenger's syndrome and two with primary pulmonary hypertension (Table 1). All patients had been catheterized for diagnostic purposes, but not in immediate connection with the tomographic study. No detailed comparison could therefore be made between the tomographic findings and the hemodynamic data. A recatheterization was not considered justifiable. The patients were ambulant and all but one were in stable condition. The exception, patient No. 9, with Eisenmenger's syndrome had sustained two episodes of hemoptysis, the last being three weeks prior to the tomographic study. None of the patients was in congestive heart failure or had any known primary airways disease.

The study was approved by the local research ethics committee, and written informed consent was obtained from each patient.

Table 1. Details of the patients studied.

Patient	Sex	Age	Diagnosis	$\overline{\text{PAP}}$	$\dot{\text{Q}}_{\text{p}}/\dot{\text{Q}}_{\text{s}}$
Group 1					
1	M	18	ASD	16	1.4
2	F	46	ASD	20	2.0
3	M	33	ASD	-	-
4	F	18	VSD	14	2.5
5	F	57	VSD	13	1.8
Group 2					
6	M	22	VSD, E	70	1.2
7	F	22	VSD, E	70	-
8	M	50	VSD, E	75	-
9	M	19	VSD, PDA, E, PI	-	-
10	M	32	PDA, E	100	0.5
11	F	45	PPH	45	1.0
12	M	22	PPH	90	0.8

$\overline{\text{PAP}}$ = mean pulmonary artery pressure at rest

$\dot{\text{Q}}_{\text{p}}/\dot{\text{Q}}_{\text{s}}$ = ratio of pulmonary to systemic blood flow

ASD = atrial septal defect

VSD = ventricular septal defect

E = Eisenmenger's reaction

PDA = patent ductus arteriosus

PPH = primary pulmonary hypertension

PI = pulmonary infarction

Hemodynamic data from patients Nos. 3 and 9 were not available for review.

METHODS

We employed a tomographic technique, using an external source of positron emitting isotope for a measurement of the density of the lung and the positron emitting isotope ^{11}C in the form of carbon monoxide as a blood pool marker. The technique has been described in detail elsewhere (2), and only a short summary is therefore presented.

Positron tomography is based on coincidence detection of the pair of γ -rays originating from the annihilation of a positron. In the instrument used (ECAT II, EG&G ORTEC), annihilation events are recorded between pairs of detectors placed in a hexagonal array around the supine patient. The information is fed to a computer and subsequently used to reconstruct a transverse plane through the object in a way similar to that used in X-ray computed tomography.

PROTOCOL

In each study, two measurements were made with the patient in the supine position. An external ring source containing positron emitting isotope ($^{68}\text{Ge}/^{68}\text{Ga}$) was placed between the patient and the array of detectors and a transmission tomogram recorded (Fig. 1, upper left panel). This shows the regional distribution of density in the chosen plane through the chest, and provides a quantitative measurement of the density of the lung (g lung/ml thoracic volume). Tomograms were obtained at two levels of the chest, at approximately the sternal insertion of the fourth rib and 8.5 cm in the cranial direction.

Following this measurement, the patient inhaled a quantity of ^{11}C -carbon monoxide in order to label the blood. After the inhalation, five minutes were allowed for mixing before emission tomograms were obtained at the same two levels. During the measurements venous blood samples were obtained and the concentration of ^{11}C -carbon monoxide subsequently measured in a well counter. The tomograms showed the regional distribution of the isotope, i.e. the distribution of blood volume (Fig. 1, upper right panel). The count density in the tomogram together with a cross calibration between

the well counter and the ECAT provided a quantitative measurement of the fractional blood volume of the lung (ml blood/ml thoracic volume).

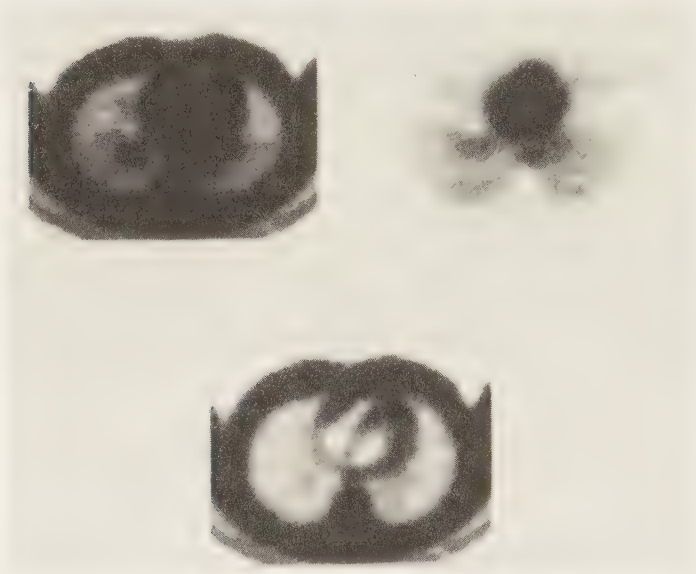


Fig. 1. Tomograms of lung density (top left panel), fractional blood volume (top right panel) and extravascular lung density (bottom panel) of a normal subject. Note the ventrodorsal gradient in lung density and fractional blood volume.

DATA ANALYSIS

The tomograms yield quantitative information about the regional density of the lung and its fractional blood volume. The extravascular density of the lung (lung tissue and interstitial water per unit thoracic volume) was calculated by subtracting the fractional blood volume from the lung density (Fig. 1, bottom panel).

The in-plane resolution and the slice thickness of the tomograms are both 17 mm full width at half maximum (FWHM). The analysis of regional

differences was done by selecting regions of interest in the lung field. Ventrodorsal differences (vertical in the supine subject) were analyzed in a 1.7 cm wide vertical strip through the right lung extending from the anterior to the posterior chest wall (Fig. 5, inset). The length of the region was normalised into ten sections so as to allow for differences in lung size. Because of the limited spatial resolution, the extreme parts of the region, sections 1 and 10, were influenced by the chest wall (partial volume effect) (3) and therefore disregarded. The ventrodorsal differences in lung density and fractional blood volume were also expressed as the ratio between the mean value in the ventral half of the region (sections 2 to 5) to that in the dorsal half (sections 6 to 9). The cranial and caudal parts of the lung were compared by selecting regions of equal size in the middle of the right lung field in each plane at the same ventrodorsal level. For comparison with data from the literature, it was desirable to obtain measurements from a large proportion of the lung. This was done by measuring mean values for lung density, fractional blood volume and extravascular lung density in the two lung fields in the caudal plane. The outline of the lung field was defined using a thresholding technique. Allowance for the influence of the chest wall was made by taking the size of the lung field into account (4). Predicted values were obtained from a group of normal subjects (see below) and the results in patients expressed as per cent of the predicted value (Table 3).

Student's t-test was used for the comparison between groups of patients and a reference group of 19 normal subjects (4), six smokers and 13 non-smokers. Their mean age was 35 years (range 20-56).

RESULTS

Tomographic distribution of lung density, fractional blood volume and extravascular lung density in a plane at the sternal insertion of the fourth rib in a normal subject is shown in Fig. 1. As previously described (2, 4), there is a ventrodorsal gradient of lung density (top left panel) in the supine subject. This is accounted for mainly by regional variations in fractional blood volume (top right panel), extravascular lung density having a more uniform distribution (bottom panel).

Illustrative tomograms from a patient with an atrial septal defect and left-to-right shunt (patient No. 1) are shown in Fig. 2. Lung density is higher in this patient than in the normal subject. Intrapulmonary blood volume is increased, while extravascular lung density appears normal.



Fig. 2. Tomograms of lung density (top left panel), fractional blood volume (top right panel) and extravascular lung density (bottom panel) of a patient with left-to-right intracardiac shunt. Lung density and fractional blood volume is increased, and the ventrodorsal gradient is less than in normal subjects.

Illustrative tomograms from a patient with Eisenmenger's syndrome are shown in Fig. 3. The right lung field (left in the image) demonstrates findings typical for the patients in group 2. There are small differences compared to the normal subjects. In the left lung in the patient, there is a wedge-shaped area of increased density in the posterior part of the lung field. This patient had a recent history of hemoptysis, and a chest radiograph (Fig. 4) showed an area of consolidation in the left lower lobe. A clinical diagnosis of pulmonary infarction had been made. Fractional blood volume is reduced in the largest part of the high density region (Fig. 3), but at the ventral edge of the region there is a localised increase in blood volume. This is likely to be an artifact; it may be due to recent haemorrhage or reflect a volume of stagnant blood. Localised high density regions were not seen in any other patient.



Fig. 3. Tomograms of lung density (top left panel), fractional blood volume (top right panel) and extravascular lung density (bottom panel) of a patient with Eisenmenger's syndrome. In the left lung field (right in the image) there is a localised region with increased density - see text.



Fig. 4. Chest X-ray of patient No. 9 with Eisenmenger's syndrome.

Results of the analysis of ventrodorsal differences in lung density, fractional blood volume and extravascular lung density are shown in Fig. 5. In the patients with increased pulmonary blood flow (group 1) lung density is increased relative to normals throughout the lung, but statistical significance is reached only in the ventral part of the lung. The increase in lung density is accounted for by a high fractional blood volume. Extravascular lung density does not show any significant deviation from normal.

In patients with high pulmonary pressure (group 2), the distribution of lung density and blood volume also tends to be more uniform than in normal subjects, but in no individual segment does the deviation from normal attain statistical significance. Extravascular lung density is normal.

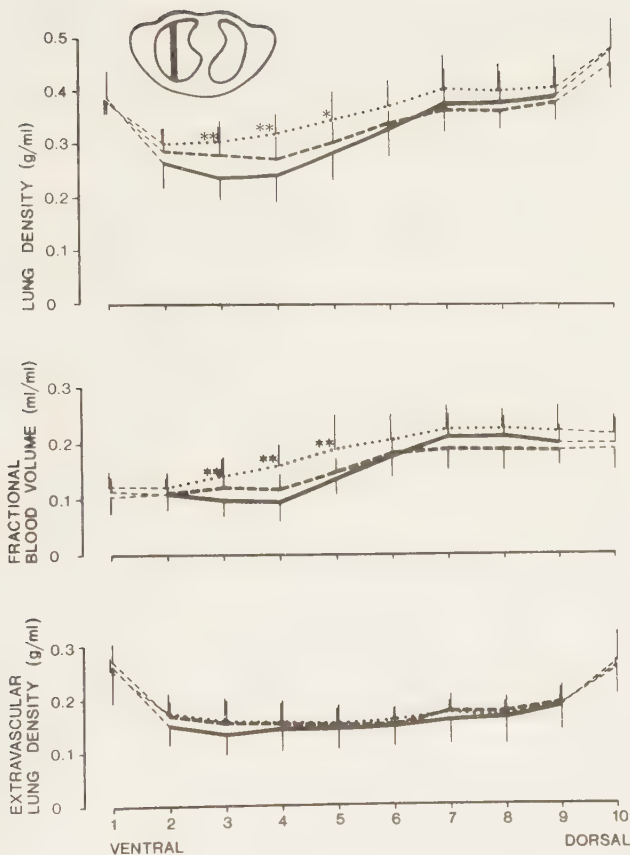


Fig. 5. Ventrodorsal gradient of lung density (top panel), fractional blood volume (middle panel) and extravascular lung density (lower panel) in normal subjects (continuous line), patients in group 1 (dotted line) and patients in group 2 (interrupted line). Measurements were made in a region of interest through the right lung field (inset). The length of the region was normalised to ten. Segments 1 and 10 are influenced by "spill-over" from the chest wall. Vertical bars indicate one SD and asterisks significant deviations from normal (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$).

When the ratio between the ventral (segments 2-5) and dorsal (segments 6-9) half of the region was regarded, lung density and fractional blood volume were found to have a significantly more uniform distribution in both groups of patients than in normal subjects (Table 2).

Table 2. Difference in lung density and blood volume between dependent and non-dependent parts of the lung.

		Ratio ventral to dorsal lung		
		LD	FBV	ELD
Group 1	mean	0.80 ⁺	0.70 ⁺	0.93
	SD	0.05	0.15	0.14
Group 2	mean	0.78*	0.65*	0.92
	SD	0.08	0.10	0.18
Normal subjects	mean	0.69	0.55	0.87
	SD	0.07	0.08	0.10

LD = lung density

FBV = fractional blood volume

ELD = extravascular lung density

Asterisks denote significant deviations from normal:

* $p < 0.05$, + $p < 0.01$

Results of the comparison between cranial and caudal lung regions at the same height are shown in Fig. 6. Patients in group 1 have increased lung density at both levels, caused by an increase in intravascular volume. The changes in group 2 are small.

In order to obtain indications of the over-all abnormalities in intrapulmonary blood volume in the patients, the mean value for the entire right and left lung fields in the caudal plane was measured. The values obtained are presented in Table 3 as per cent of the predicted normal value. A significant increase in fractional blood volume was found in the patients with high pulmonary blood flow (group 1). In the patients

with high pulmonary vascular pressure, small increases in lung density, fractional blood volume and extravascular lung density were found.

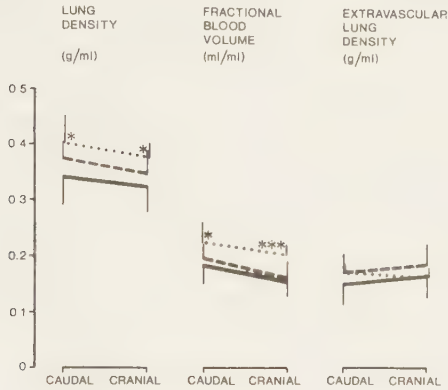


Fig. 6. Cranio-caudal differences in lung density (left panel), fractional blood volume (middle panel) and extravascular lung density (right panel) in normal subjects and patients. Regions of interest of equal size were chosen at the same vertical height in the right lung fields in the two planes. Symbols as in Fig. 5.

Table 3. Mean lung density, fractional blood volume and extravascular lung density measured in the lung fields in the caudal plane.

		LD (% pred)	FBV (% pred)	ELD (% pred)
Group 1	mean	103.6	115.2*	96.7
	SD	3.9	12.8	9.3
Group 2	mean	105.1*	103.8	104.9*
	SD	7.0	18.7	4.3
Normal subjects	mean	100.0	100.0	100.0
	SD	4.5	11.4	5.5

Symbols as in Table 2.

DISCUSSION

Regional pulmonary blood flow has been studied extensively in experimental situations as well as in clinical conditions, and a model has evolved (5-8) which relates regional blood flow to arterial, alveolar and venous pressures. Large regional variations in perfusion with vertical height have been described in the lung in normal, resting man (9, 10). The regional differences are smaller in situations with increased pulmonary blood flow, such as exercise (10) and intracardiac left-to-right shunting (11). Abnormally uniform pulmonary perfusion has also been found in patients with pulmonary arterial hypertension without over-all increase in blood flow (11).

Although the model describing the relation between pressures and flow in the pulmonary circulation implies regional increases in blood volume, no quantitative measurements of the regional distribution of pulmonary blood volume in man in situations with increased pulmonary blood flow or pulmonary arterial hypertension are available.

In this study, we have measured the regional distribution of pulmonary blood volume in a group of patients with intracardiac left-to-right shunts, i.e. patients with increased pulmonary blood flow in connection with no or slight pulmonary hypertension. The second group comprises patients with Eisenmenger's syndrome and patients with primary pulmonary hypertension. In Eisenmenger's syndrome, the structural lesions in the pulmonary vasculature are of the same nature as in primary hypertension (12). Pulmonary artery pressure is elevated to systemic levels, and the shunt is often bidirectional with an average pulmonary to systemic flow ratio close to unity (13). We therefore think it is appropriate to include both categories of patients in one group, characterized by high pulmonary arterial pressure and normal or reduced blood flow.

The tomographic technique used in the study provides accurate measurements of fractional pulmonary blood volume (2). Only blood contained in intrapulmonary vessels is included in the measurement. Regional extravascular density of the lung (lung tissue and interstitial water per unit thoracic volume) can also be calculated. This was of interest especially in the patients in group 2, as it suggests the possibility of detecting structural lesions in the pulmonary vasculature noninvasively.

We found the distribution of pulmonary blood volume to be more uniform in both patients groups than in normal subjects. In similar groups of patients, Dollery and coworkers (11) have described an abnormally uniform distribution of pulmonary blood flow. The two studies thus suggest parallel changes in regional pulmonary blood flow and volume, which may be explained by dilatation (14) and/or recruitment (15) of vessels.

Fractional pulmonary blood volume was increased in patients with intracardiac, left-to-right shunts. The possibility that this measurement is influenced by abnormal lung inflation has to be considered. A previous study (16) has failed to demonstrate any abnormalities in lung volumes in patients with intracardiac septal defects. Furthermore, any changes in lung inflation would be accompanied by changes in extravascular lung density, as this reflects the amount of lung tissue and interstitial water per unit thoracic volume. Our finding of normal extravascular lung density in the patients therefore indicates that the observed abnormalities in fractional pulmonary blood volume represent a true increase in intrapulmonary blood volume which is of the order of 15 % or 0.03 ml/ml. In

patients with cardiac septal defects and normal pulmonary vascular resistance, Bucci and Cook (17) found an average increase in capillary blood volume of 70 %, which, assuming a normal capillary blood volume of 75 ml and a thoracic volume of 3 ℓ, would correspond to an increase in fractional pulmonary blood volume of about 0.02 ml/ml. In view of this, a large part of the increase in pulmonary blood volume we observed in patients with increased pulmonary blood flow could be explained by recruitment or distension of capillary beds. This would imply that distention of larger vessels is less important, which is in agreement with experimental observations (15).

In the patients with severe pulmonary hypertension and normal or reduced blood flow, we found small increases in lung density, fractional blood volume and extravascular lung density. Although this may reflect increases in intrapulmonary blood volume and reactive tissue changes in the pulmonary vasculature or parenchyma, we can not exclude that such small changes may result from a reduction in lung inflation. Small reductions in lung volumes have also been described in patients with Eisenmenger's syndrome (18). The results of the measurements of fractional blood volume in the two groups of patients suggest that intrapulmonary blood volume falls with the development of pulmonary hypertension and decline in pulmonary blood flow in patients with intracardiac shunts. This may be due to a reduced compliance of the pulmonary vessels or to obliteration of capillary beds.

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MEASUREMENT OF PULMONARY ERYTHROMYCIN CONCENTRATION IN PATIENTS WITH LOBAR PNEUMONIA BY MEANS OF POSITRON TOMOGRAPHY

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Summary The concentration achieved in the infected tissue is of fundamental importance in the use of antibiotics. Erythromycin labelled with the positron-emitting nuclide carbon-11 and positron tomography were used to compare local concentrations of this antibiotic in the pneumonic and unaffected lungs of five patients with lobar pneumonia. The time course of uptake of erythromycin into the extravascular compartment (i.e., the intracellular, interstitial, and alveolar compartments) of the pneumonic lung was measured. The mean extravascular concentrations obtained during the first hour after an intravenous injection of 270 mg erythromycin lactobionate were similar in the pneumonic lung and the unaffected lung (5.5 ± 2.2 and 6.6 ± 2.2 $\mu\text{g/g}$, respectively). An effective concentration of erythromycin was reached in the pneumonic lung within 10 min of the injection and was maintained throughout the period of measurement (60 min).

Introduction

ALTHOUGH antibiotics have dramatically reduced mortality from lobar pneumonia, there is still considerable mortality from pneumococcal pneumonia, particularly in elderly patients.¹ One explanation for this finding might be that the rate of entry of antibiotics into pneumonic lung is low. Antibiotic concentrations in resected normal lung tissue have been measured,^{2,3} but most studies of antibiotic penetration to the respiratory tract in human beings have been based on comparisons of blood and sputum antibiotic levels.⁴ Because of the lack of non-invasive techniques, the rate of penetration and the concentration of antibiotic achieved in pneumonic lung remain unknown.

The development of positron-emission tomography made possible measurement of the local concentration of a positron-emitting radionuclide sequentially and non-invasively.^{5,6} We labelled erythromycin with positron-emitting carbon-11 (half-life 20.4 min) without changing its biochemical characteristics,⁷ and we followed the local

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concentration after an intravenous injection of the labelled antibiotic in man. We now describe the time course of uptake of erythromycin into the extravascular compartment of consolidated lung and unaffected lung in five patients with acute lobar pneumonia.

Patients and Methods

Patients

Five patients with acute lobar pneumonia were studied in the first few days of their illness. Diagnosis was based on usual clinical and radiological criteria, and evidence of the causative micro-organism was sought by sputum and blood culture and by serological tests, which allowed a positive microbiological diagnosis to be made in three patients (see table). All five patients had been treated with antibiotics before the study. All subsequently made a satisfactory recovery with reduction of symptoms and radiological abnormalities.

The investigation was approved by the research ethics committee at the Royal Postgraduate Medical School and informed written consent was given by each patient. The estimated radiation dose was approximately 1 rad (10 mGy) to the blood (critical organ).

Methods

Preparation of ^{11}C -erythromycin lactobionate (^{11}C -E).—Full details of the labelling procedure are presented elsewhere.⁷ Briefly, erythromycin was labelled at the dimethylamino group of the D-desosamine portion of the molecule by reductive methylation of *N*-demethylerythromycin with ^{11}C -formaldehyde. The latter was prepared from cyclotron-produced ^{11}C -carbon dioxide by a method similar to that of Christman et al.⁸ Rapid purification of the ^{11}C -E was achieved by high-pressure liquid chromatography. Purified ^{11}C -E was made up as a solution of the lactobionate salt (20 mg) in 5% dextrose (5.0 ml) and sterilised by filtration (0.22 μm pore size).

Positron tomography measurements were made with an EG&G Ortec ECAT II scanner on patients in the supine position. Three different tomographic measurements were made through the same transaxial plane in each patient. The plane was selected with the help of the chest radiograph to go through the consolidated region of the lung. First, a transmission scan was carried out with an external ring source containing positron-emitting gallium-68/germanium-68. This tomogram provided a measurement of the physical density of the lung and information for attenuation correction of the ensuing emission scans. Next, 2–4 mCi of ^{11}C -E immediately followed by 250 mg non-radioactive erythromycin lactobionate in 25 ml dextrose solution were injected intravenously. The total amount of erythromycin lactobionate administered was approximately 270 mg. 5 min were allowed for the ^{11}C -E to mix in the blood pool, and six sequential emission tomograms, each lasting 10 min were then obtained. Finally, ^{11}C -carbon monoxide in air was inhaled in order to label the blood pool. Care was taken to obtain a count-rate ratio over the chest of at least 10/1 between ^{11}CO and residual ^{11}C -E. A final emission scan was then carried out to measure the regional distribution of pulmonary blood volume. During the scan, three venous blood samples were taken and the concentration of ^{11}CO in the blood was measured in a well counter.

Data analysis.—The initial transmission scan provided a measurement of the lung density (expressed in g/ml thoracic

CLINICAL DATA AND MEAN ERYTHROMYCIN CONCENTRATIONS IN PNEUMONIC AND UNAFFECTED LUNG

Patient	Sex	Age (yr)	Duration of symptoms (days)	Location of pneumonia	Causative micro-organism	Total extravascular erythromycin concentration			
						($\mu\text{g/ml}$)*		($\mu\text{g/g}$)†	
						Infected	Control	Infected	Control
1	M	64	8	Right upper lobe	<i>Mycoplasma pneumoniae</i>	2.27	0.97	4.34	5.14
2	F	79	4	Right lower lobe	<i>Streptococcus pneumoniae</i>	1.34	0.71	2.68	4.30
3	F	64	2	Left lower lobe	Not identified	2.28	1.18	7.66	7.62
4	F	74	5	Right upper and lower lobe	<i>Streptococcus pneumoniae</i>	2.42	0.66	5.26	4.77
5	M	62	4	Right lower lobe	Not identified	2.88	0.57	7.70	9.49
Mean $\pm$ SD						2.24 $\pm$ 0.56	0.82 $\pm$ 0.25	5.52 $\pm$ 2.16	6.62 $\pm$ 2.22

*Extravascular concentration expressed in $\mu\text{g/ml}$ thoracic volume.†Extravascular concentration expressed in $\mu\text{g/g}$ extravascular lung (intracellular, interstitial, and any alveolar fluid).

volume) within the chosen transaxial plane. The set of six sequential emission scans measured the regional ^{11}C -E concentration in $\mu\text{Ci/ml}$ thoracic volume. The final emission scan obtained after labelling the blood with ^{11}CO gave a measurement of regional blood volume, which can be expressed in g/ml or $\mu\text{Ci/ml}$ thoracic volume. From these data, the concentration of ^{11}C -E in the extravascular compartment (i.e., intracellular and interstitial space plus the alveolar compartment) was calculated and expressed either as $\mu\text{Ci/ml}$ thoracic volume or as $\mu\text{Ci/g}$ in the extravascular compartment. For the calculations, the values of lung density and concentrations of ^{11}C -E and ^{11}CO were taken as the mean picture element count in a large ($14\text{--}30\text{ cm}^2$) region of interest in the centre of each lung field. In each patient the regions were the same size on each occasion, and they were defined in the transmission tomogram before being applied to the other measurements.

Calculation of extravascular lung density has been described in detail elsewhere.⁹ Briefly, both lung density (transmission) and the blood volume tomograms were expressed in g/ml thoracic volume; subtraction of the contribution of blood to the overall density of the lung yielded the extravascular density in g/ml thoracic volume.

Calculation of extravascular erythromycin concentration.—In an analogous way, we subtracted the contribution of circulating ^{11}C -E from the six sequential ^{11}C -E tomograms using the blood volume measurement. The two measurements were normalised to the count density in arterial blood, as measured from a region of interest in the aorta or in the left heart. The region was $1.2\text{--}2.9\text{ cm}^2$ and was delineated in the blood-volume scan before being projected on to the ^{11}C -E scans. This subtraction gave extravascular ^{11}C -E per unit thoracic volume ($\mu\text{Ci/ml}$). Dividing this by the extravascular lung density (g/ml), the extravascular radioactivity can be expressed per unit extravascular lung mass ($\mu\text{Ci/g}$). On the assumption that radioactive and non-radioactive erythromycin were distributed identically, the total drug concentrations in the extravascular compartment were calculated in units of $\mu\text{g/ml}$ thoracic volume and $\mu\text{g/g}$ extravascular lung mass.

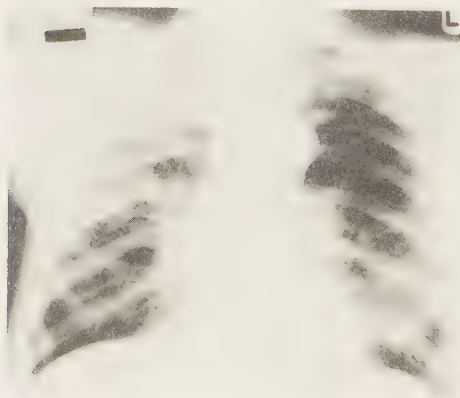


Fig. 1—Chest radiograph of patient 1, showing right upper-lobe pneumonia.

Results

The postero-anterior radiograph, extravascular lung density tomogram, and $^{11}\text{C-E}$ tomogram of patient 1 are shown in figs 1 and 2. The extravascular lung density tomogram showed an increase in lung density corresponding to the pneumonic consolidation seen in the radiograph. The mean extravascular lung density in the pneumonic lung in the five patients was $0.43 \pm \text{SD } 0.09$ and that in the unaffected lung was 0.14 ± 0.05 g/ml. Regional blood volume was variable, most patients showing some fall in blood volume in the consolidated region. The $^{11}\text{C-E}$ tomogram in fig. 2, which has been corrected for circulating $^{11}\text{C-E}$, shows that the extravascular $^{11}\text{C-E/ml}$ thoracic volume was higher in the pneumonic lung than in the unaffected lung.

The mean total concentrations (radioactive plus non-radioactive) of erythromycin in the extravascular lung

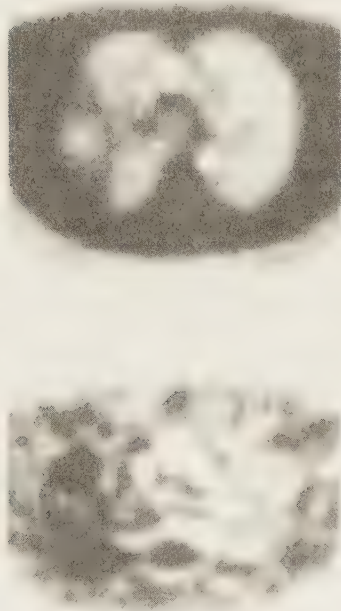


Fig. 2—Tomogram showing regional distribution of extravascular lung density (upper panel) and extravascular $^{11}\text{C-E}$ (lower panel).

Note (upper panel) increase in density (darker region) in the right upper lobe (left). Radioactivity/unit volume (lower panel) is higher (darker region) in pneumonic than in unaffected lung.

compartment during the period of measurement are given in the table. When expressed in μg per ml thoracic volume, the concentration was significantly higher in the infected lung than in the unaffected lung ($p < 0.001$, unpaired t test). This measurement was, however, clearly influenced by the higher density of the pneumonic lung. Division by extravascular lung density allowed the concentration of erythromycin in the extravascular compartment of the lung to be expressed in $\mu\text{g/g}$, and then the concentration in the pneumonic lung and the unaffected lung were not significantly different.

The mean time for clearance of ^{11}C -E from arterial blood and uptake into the pneumonic lung for the five patients is shown in fig. 3. In each patient, the extravascular concentration of ^{11}C -E has been normalised to the initial concentration in arterial blood, assuming a monoexponential clearance of activity from the blood. There was a rapid uptake of erythromycin into both the pneumonic and the unaffected lung, effective concentrations being reached within 10 min of the injection. Blood and lung concentrations reached equilibrium after approximately 45 min, and thereafter the extravascular concentration of the drug started to fall.

Discussion

Previous measurements of antibiotic concentration in lung tissue have been made on specimens obtained at surgery.^{2,3} Most such measurements have been made in normal lung; only a single measurement was therefore obtained and the sample was inevitably contaminated with blood. In contrast,

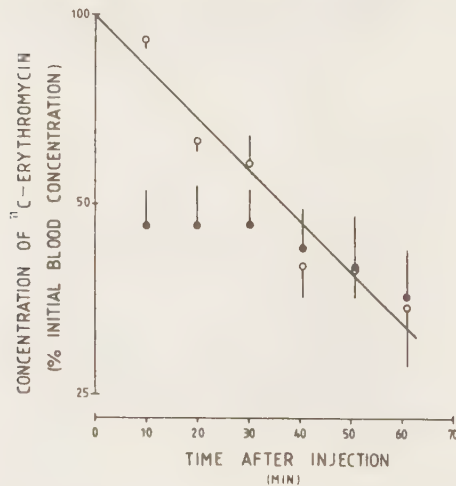


Fig. 3—Blood clearance and uptake of ^{11}C -erythromycin into the extravascular compartment of the pneumonic lung.

Open circles = mean $\pm$ SE of arterial blood concentration in five patients. Equation: $\ln y = 10.0x + 4.60$, $r = 0.96$. Closed circles = mean $\pm$ SE of extravascular concentration in pneumonic lung.

our non-invasive technique allows extravascular concentrations to be measured sequentially in both normal and pneumonic lung.

We believe that the positron-emission tomography technique gives an accurate measurement of erythromycin in the lung. The labelling of erythromycin with carbon-11 involves substitution of a carbon atom but does not change the chemical structure of the drug.⁷ The quantitative accuracy of positron tomography for measuring the concentration of positron-emitting isotopes and soft-tissue density is well established. Owing to the low density of the lung, counting statistics will always be a limiting factor for measurements of pulmonary-tissue concentration of labelled compounds. The amount of radioactive isotope we used did not allow detailed regional measurements of erythromycin concentration. However, by selecting sufficiently large regions of the lungs for study satisfactory measurements can be made. The statistical accuracy of our measurements of ¹¹C-E, regional blood volume, and lung density has been assessed from a phantom study.⁹ Assuming that the standard deviation of a measurement in a given area in the tomogram is a square-root function of the number of coincidence events accumulated, we estimate the coefficient of variance in repeated measurements of ¹¹C-E to be less than 2.0%, in the measurements of regional blood volume less than 0.8%, and in the measurement of lung density less than 1.7%.

There was rapid uptake of intravenously injected erythromycin into both normal and pneumonic lung so that within 10 min of injection antibiotic concentrations were well above the minimum inhibitory concentration for most sensitive organisms.¹⁰ At the levels reached erythromycin is bacteriocidal for the more sensitive strains¹¹ and is effective against *Mycoplasma pneumoniae*. Although we did not find any significant overall difference between erythromycin concentrations in pneumonic and unaffected lungs, the extravascular concentration measured in pneumonic lung is a volume-weighted mean of erythromycin in intracellular, interstitial, and alveolar compartments, which may have differing erythromycin concentrations. In two previous studies^{2,3} erythromycin concentrations were measured by microbiological assay in homogenised lung tissue obtained at surgery from patients who had been treated preoperatively with oral erythromycin, 0.5 g three times daily. The concentration found in these studies accords with our results, but precise comparison is not possible owing to the different routes of administration. In one study,³ lung tissue concentration was also measured 3 h after injection of 500 mg erythromycin lactobionate; the value (6.53 µg/g) is compatible with ours (6.6 µg/g) during the first hour after injection of 270 mg erythromycin lactobionate. Results of previous studies of the pharmacokinetics of erythromycin, based on a two-compartment model, also suggest a fast exchange between the central and the peripheral

compartment, with an apparent distribution volume comparable to total-body-water volume.¹²⁻¹⁴

To the best of our knowledge, our studies are the first direct measurements of the uptake and concentration of an antibiotic in infected lung in human beings. The results indicate that erythromycin penetrates rapidly and in effective concentrations into areas of acute pneumonia. The technique should be useful for the in-vivo study of other drugs used in lung disease.

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